Identifying Gaps Using the EPICOT+ Framework and Exploring the Association between Funding Sources and Author Conclusions in Primary Nutrition Research Addressing Non-communicable Diseases from Cochrane Nutrition Reviews: A descriptive-analytical cross-sectional study

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March 2021

Research assignment presented in partial fulfilment of the requirements for the degree of Master of Science (Clinical Epidemiology) in the faculty of Medicine and Health Sciences at Stellenbosch University

Declaration of financial assistance: I hereby acknowledge financial assistance from Prof Lisa Bero, recipient of the 2015 Cochrane Anne Anderson Award, whereby a cash sum is designated by the recipient to assist a woman from a low-resource setting with Cochrane activities. I hereby acknowledge receiving a bursary from Novartis SA (Pty) Ltd, which was used to cover the cost of my Master of Science (Clinical Epidemiology) tuition fees. Opinions expressed and conclusions arrived at, are those of the authors and are not necessarily to be attributed to Cochrane or Norvatis SA (Pty) Ltd.

This manuscript was drafted for submission to the BMC Research Methodology Journal

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Signature: Sheena Ruzive Date: 01 March 2021

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Identifying Gaps using the EPICOT+ Framework and Exploring the Association between Funding Sources and Author Conclusions in Primary Nutrition Research Addressing Non-communicable Diseases from Cochrane Nutrition Reviews: A descriptive-analytical cross-sectional study

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Abstract

Background:

With the rise in non-communicable diseases (NCDs) globally, we aimed to summarise the research gaps and describe the adequacy of the reporting of future research recommendations in Cochrane reviews of nutrition interventions addressing NCDs. We also aimed to explore the influence of funding sources and author- sponsor financial ties on author conclusions in a subset of primary studies included in these reviews.

Methods:

Two researchers independently screened a Cochrane nutrition reviews database (n=470, July 2015) to identify reviews addressing four NCDs (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes). The "implications for research" section of eligible reviews was analysed using the evidence, population, intervention, comparison, outcome, timeframe, study design and burden of disease (EPICOT+) framework to describe the extent of reporting of research recommendations and to summarise gaps. A purposive sample of English full-text studies included in reviews addressing alternative nutrition supplements were analysed to assess reporting of conflict of interest (COI), funding sources and author-sponsor financial ties, and to explore influences of funding sources and author-sponsor financial ties on author conclusions.

Results:

Ninety-eight eligible reviews were analysed. The EPICOT+ reporting was as follows: evidence 34/98 (33.7%), population 68/98 (69.4%), intervention 90/98 (91.8%), comparison 26/98 (26.5%), outcomes 78/98 (79.6%), study design 85/98 (86.7%), time frame 52/98 (53.1%), and burden of disease 7/98 (7.1%). Studies requiring better quality, different interventions, and outcomes in low- and middle-income countries (LMICs) were highlighted. Seven reviews addressed alternative nutrition supplements, including 51 eligible primary

studies. Conflicts of interest were disclosed in 10/51 (19.2%); funding in 27/51 (51.9%), of which, 11/27 (40.7%) were industry and 16/27 (59.3%) were non-industry sponsors; and author-sponsor financial ties in 9/51 (13.4%), of which 1/9 (11.1%) was industry and 8/9 (88.9%) were non-industry. There was no association between authors making favourable conclusions and having industry sponsors and author-sponsor financial ties (8/12) compared with non-industry sponsors and no author-sponsor financial ties (10/24), (Fisher exact p =0.289).

Conclusions:

EPICOT+ items were not well reported in most reviews. Future studies of better quality, different interventions, outcomes or populations in LMICs are needed. Authors should disclose all COI, funding sources and author-sponsor financial ties. Possible influences of funding sources and author-sponsor financial ties on author conclusions needs further investigation.

Keywords: Non-communicable diseases, Nutrition, Cochrane systematic reviews, Research recommendations, EPICOT+ Framework, Conflicts of interest, Funding

Background

Non-communicable diseases: burden and risk factors

Non-communicable Diseases (NCDs) are medical conditions that are non-infectious and not transmissible between people (1). Non-communicable Diseases are commonly categorised into the following groupings: cardiovascular diseases, cancer (all types), chronic respiratory diseases (e.g. asthma, bronchitis), diabetes (type 1 and 2), renal disease, endocrine disease, neurological disorders, haematological disorders (e.g. sickle cell anaemia), gastroenterological disease (e.g. peptic ulcers), hepatic disease (e.g. liver cirrhosis), musculoskeletal disorders, skin diseases, oral diseases, genetic disorders, mental disorders, optometry disorders and deafness (2). The four major groups that contribute to over 80% of deaths from NCDs are cardiovascular diseases, cancer, chronic respiratory diseases and diabetes (1). In 2018, NCDs accounted for 41 million deaths globally (3). Annually, about 15 million people die prematurely (people between age of 30-69) from a NCD and over 85% of these "premature" deaths occur in LMICs (3). The WHO aims to reduce premature mortality from NCDs by one-third through prevention and treatment and it recommends that governments and stakeholders adopt effective interventions to halt this global rise in NCDs (2).

Risk factors associated with NCDs largely stem from unhealthy lifestyles and exposure to adverse physical and social environments. Modifiable risk factors include unhealthy diets, direct and passive smoking, other uses of tobacco, physical inactivity, excessive use of alcohol and psychological stress (4–7). Poor nutrition during pregnancy and childhood also predisposes individuals to develop NCDs in adulthood (8,9). Knowledge of the modifiable risk factors contributing to NCDs presents an opportunity to find effective interventions to reduce the incidence of NCDs (4).

A vast body of observational and experimental evidence has shown that people with healthier diets have a lower risk of developing NCDs. A meta-analysis of nine cohort studies (n=91,379 men and n=129,701 women) reported that the risk of developing coronary heart disease decreased by 4% for each additional portion per day of fruit and vegetable intake and decreased by 7% [RR (95%CI): 0.93 (0.89–0.96), P<0.0001] for fruit intake (5). Vegetable intake also reduced the risk of mortality [RR (95%CI): 0.74 (0.75–0.84),

P<0.0001] and fatal and nonfatal myocardial infarctions [RR (95%CI): 0.95 (0.92–0.99),P<0.0058] (5). Another systematic review of randomised control trials (RCTs) found that reducing the consumption of dietary saturated fat reduced the risk of cardiovascular events by 17% [RR (95%CI) 0.83 (0.72 to 0.96)] in individuals regardless of whether they had a previous cardiovascular event or not (10). The evidence from these and other studies demonstrates the potential for lifestyle interventions, including those addressing dietary risks, to prevent NCDs (11–13).

In light of the above evidence and the need to adopt interventions that are effective in halting the rise in NCDs globally, and especially in LMICs, the WHO proposed a Global Action Plan for the prevention and control of NCDs (2). This action plan highlights the need to use strategies based on the latest scientific evidence and/or best practice, cost-effectiveness, affordability and public health principles, while ensuring that recommendations are culturally acceptable (2).

Systematic reviews as sources of evidence and to identify research gaps

The best available evidence is commonly considered to be from rigorously conducted and reported systematic reviews (14). Cochrane systematic reviews are regarded as high quality sources of synthesised scientific evidence, as they follow robust and standardised methodology (15). Cochrane systematic reviews attempt to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question (16).

In Cochrane reviews, authors are required to include sections about the implications for practice and research in light of the evidence that has been synthesised in the review; information that is used increasingly often by people making decisions about future research (16). The “implications for research” section should include information about the need for further research, as well as the desirable nature of this research (16). Even though the extent to which this section is completed in Cochrane reviews is variable, most reviews identify residual uncertainty and are a rich source of suggestions for further research (17). Analysing the content of the “implications for research” section of Cochrane reviews can help inform primary research gaps, as well as identify interventions for which the evidence is conclusive and thus do not

require further research (18). The problem, however, is the variability in formulating and reporting research recommendations by different systematic review authors (19).

The EPICOT+ framework was developed to provide a means of standardised reporting of recommendations under the "implications for research" section of reviews (20). According to the EPICOT+ framework, research recommendations should be made in consideration of the current state of evidence (E) found by a thorough up to date literature search, the number of systematic reviews and primary studies being analysed and the total number of the participants from the reviews. Other factors to consider when making recommendations include the population (P) being studied (type of participants, their age, race, gender, comorbidities and specific inclusion criteria), the intervention (I) being tested (type, dose, frequency, duration), the comparison (C) (placebo, other drugs or no intervention, duration), the outcome of interest (O) and the time frame (T) (i.e. the length of follow up of participants and duration of future primary studies). The "+" refers to the study design and the burden of the disease of interest, which are additional elements to be considered and stated clearly when formulating recommendations. Apart from allowing for the formulation of recommendations in a standardised manner, using the EPICOT+ framework ensures that recommendations for future research are specific and explicit and thus more useful (20). For any future primary research it is also important that it clearly reports potential authors' funding and conflicts of interest, as previous studies have shown that financial ties between study authors and funders may influence how authors interpret study findings (21,22).

Reporting conflicts of interest in Cochrane Reviews

For valid interpretation and application of systematic review findings, high methodological quality is a prerequisite. A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) has been developed to assess the methodological quality of systematic reviews , which has been tested and shown to have good agreement, reliability, construct validity and feasibility (23). The AMSTAR 2 tool aims to ensure that bias was avoided during the conduct of systematic reviews, through evaluating the methodology reported against 16 distinct criteria (24). According to the AMSTAR 2 tool checklist, items 10 and 16 require that conflicts of

interest (COI) and sources of support be clearly acknowledged in the primary studies included in the review and the systematic review (24). Conflict of interest is defined as a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain) (25).

Most systematic review authors report their COI and sources of funding for the review, however, a recent analysis found that only 21/296 (7%) reviewers reported the COI or funding sources of the primary studies included in their reviews (26). This has important implications since the outcome of the study and interpretation of study findings may be influenced by the source of funding and author-sponsor financial ties (22). Lesser and colleagues explored the relationship between financial sponsorship and study conclusions on the benefits of milk, soft drinks and juice from interventional studies, observational studies, and scientific reviews (27). None of the interventional studies that received industry funding reported unfavourable conclusions whilst 37% of the studies that did not receive industrial funding reported unfavourable conclusions about milk, soft drinks and juice consumption. A qualitative systematic review by Schott and colleagues (28), which explored the association between financing of drug trials by pharmaceutical companies and the drug trial outcomes found that trials reporting a favourable outcome were 7.61 times more likely to have received industry funding compared to the trials reporting an unfavourable outcomes. A study of published systematic reviews assessing the effect of sugar-sweetened beverages (SSB) consumption and weight gain or obesity found that the reviews that reported COI were five times more likely to present a conclusion of no positive association between SSB consumption and weight gain compared to reviews that did not report COI [RR (95%CI): 5.0 (1.3–19.3)] (29). These studies provide evidence that financial ties between study authors and funders may influence how authors interpret study findings. This highlights the need for review and primary study authors to declare their COIs and study sponsor information and affiliation when reporting studies.

With the rise in NCDs globally, there is a need to identify research gaps in the primary evidence base on nutrition interventions that may be useful to control the NCD burden. Cochrane nutrition reviews addressing NCDs provide the best scientific evidence to inform further research; however, there is a need to explore

how review authors report recommendations and identify areas that need improvement to achieve standardised and more useful reporting of recommendations. Since financial ties between study authors and funders may influence how authors interpret study findings, there is the need to assess how primary study authors report their COIs, funding sources information and author-sponsor financial ties and to explore the influence of funding sources information and author-sponsor financial ties on author conclusions in primary studies included in Cochrane nutrition reviews addressing NCDs.

Methods

Aim

We aimed to describe the reporting of the "implications for research" section using the EPICOT+ framework, to summarise research gaps identified in the "implications for research" section of Cochrane Nutrition Reviews addressing the four major groups of NCDs, namely cardiovascular diseases, cancer, respiratory disease and diabetes and their nutrition-related risk factors (e.g. obesity), as well as to assess reporting of COI, funding sources and author sponsor financial ties and exploring the influence of these funding sources on author conclusions in primary studies included in a subset of reviews addressing alternative nutrition supplements.

Objectives:

To

(1) Describe the reporting of the "implications for research" section of Cochrane nutrition reviews addressing the four major groups of NCDs, namely cardiovascular diseases, cancer, respiratory disease and diabetes and their nutrition-related risk factors (e.g. obesity) according to the EPICOT+ framework;

(2) Summarise current gaps in primary research based on the "implications for research" section of Cochrane nutrition reviews addressing the four major groups of NCDs and their nutrition-related risk factors (e.g. obesity);

(3) Assess the reporting of COI and financial sponsors in included English primary studies of Cochrane nutrition reviews addressing alternative nutrition supplements (e.g. chitosan, cinnamon, Coenzyme Q, dietary flavonoid and garlic) and the four major groups of NCDs and their nutrition-related risk factors (e.g. obesity); and

(4) Explore the influence of funding sources and author-sponsor financial ties on author conclusions in included English primary studies of Cochrane nutrition reviews addressing alternative nutrition supplements and the four major groups of NCDs and their nutrition-related risk factors (e.g. obesity).

Study Design

A descriptive analytical cross-sectional study.

Data source

The source of systematic reviews for this study was a database of Cochrane nutrition reviews compiled for a previous project, in which all active records in the Cochrane Database of Systematic Reviews (n=8484) up to 31 July 2015, were screened to identify nutrition-relevant reviews using a pre-specified definition (Box 1). A total of n=470 completed Cochrane nutrition reviews were included in the database.

Box 1: Definition used for screening and selection of nutrition reviews in the Cochrane Database of Systematic Reviews

> Nutrition reviews were defined as reviews that investigate the effectiveness of interventions of:
>
> (1) Diets and dietary patterns; foods; formulated, fortified or enriched foods or nutritional products and nutrients and bioactive non-nutrients naturally in foods delivered orally, enterally or parenterally;
>
> (2) Nutrition education, promotion, counselling and programmes; coordination of care or delivery of foods or nutrients; and
>
> (3) Any policies, programmes or systems that influence outcomes clearly distinguishable as nutrition-related (nutrition-sensitive).

EPICOT+ Framework

Selection of Cochrane nutrition reviews addressing the four major non-communicable diseases and their nutrition-related risk factors

A pair of researchers (SR and CEN/SD) independently screened the Cochrane nutrition reviews database (n=470), examining the title, and if needed the abstract and full-text to ascertain eligibility. Reviews were eligible if they addressed any of the four major groups of NCDs, namely cardiovascular diseases, cancer, chronic respiratory diseases and diabetes or their nutrition-related risk factors (e.g. obesity). Reviews were excluded if they were withdrawn or included pregnant women as participants since reviews addressing

pregnant women were beyond the scope of this project. Any disagreements on inclusion or exclusion of reviews were resolved by discussion and consensus among the three researchers. In cases where eligible reviews had been updated, the most recent updates (up to December 2020) of all the eligible reviews identified during the screening process were used for the analyses.

Data Collection

Data extraction for all reviews was performed by one researcher (SR) using a standardised and piloted data extraction form. For quality control, MV, SD and CN independently checked the data from 20% of the reviews. There was good agreement between authors. Discrepancies were resolved through discussion.

We collected the following information from the eligible Cochrane nutrition reviews: accession number, title, NCD grouping, NCD being addressed and/or nutrition-related risk factor being addressed, populations and interventions, and publication year. We extracted the following EPICOT+ items from the ”implications for research” section of all included Cochrane nutrition reviews: evidence, participants, intervention, comparison, outcomes, timeframe of the study, study design and burden of disease. If an EPICOT+ item was explicitly stated and/or explained in the “implications for research” section, we coded the item as “TRUE”. For example, we recorded TRUE for “population” for the recommendation: “More randomised trials are needed on the effects of vitamin D on cancer in younger persons, in men, and in people with low vitamin D status” (29). Table 1 shows examples for the coding for each EPICOT+ Framework item. If the element was not stated and/or explained in the “implications for research” section, we coded it as “FALSE” in the data extraction sheet. We also copied and pasted the text from the “implications for research” section to the data extraction sheet to justify the TRUE/FALSE judgements. We extracted data from the text of the “implications for research” section from each included nutrition review to i) Summarise and categorise this data into implications for research themes that will guide future research, and to

ii) Identify the specific EPICOT+ framework components of the recommendations for future research, e.g., the specific age or gender of participants or study design future research should address.

Table 1: Examples of EPICOT+ framework implications for research coding

EPICOT+ Framework item	Example of "implications for research section" EPICOT+ items coded as "TRUE" (reference)
Evidence	Given the small number of studies that have been conducted to date, there is need for research in this area. Only two studies have been conducted to date in children so it is difficult to make any firm conclusions as to the benefits, or otherwise, of marine n-3 fatty acid supplementation in this age group(30)
Population	More randomised trials are needed on the effects of vitamin D on cancer in younger persons, in men, and in people with low vitamin D status(31)
Intervention	The intervention should be designed to study pure compounds and compare outcomes with a placebo group(32)
Comparison	Future studies should ensure that innovative interventions are always compared to 'standard care(33)
Outcome	Further trials should measure important outcomes which include mortality, morbidity and quality of life.(34)
Timeframe	High quality trials with follow-up for one year or more are notably sparse(35)
Study design	International, multicentre, rigorously designed, adequately powered, long-term, high-quality studies are required to provide better evidence(36)
Burden of disease	We urge researchers and funding bodies in all countries to support research on childhood obesity in low- and middle-income countries, and better understand the experiences of nutrition transition and rapid weight gain. In the context of some countries, this research should aim to address the double burden of malnutrition.(37)

Data analysis

We used descriptive statistics and data are presented as counts and percentages, and visually, using graphs and tables.

EPICOT+ Framework

We classified the included reviews according to the NCD grouping addressed (cardiovascular diseases, cancer, chronic respiratory disease, diabetes and nutritional risk factor -obesity and healthy diets) and reported these data as counts and percentages. We tabulated the characteristics of the reviews. We reported the percentages of reviews making recommendations according to the EPICOT+ framework elements, for example, the total number of reviews that made recommendations considering the population (total number of "TRUE" for population) is expressed as a percentage of the total number of reviews included in this analysis. We also describe which EPICOT+ framework elements were better or less well reported in these reviews.

Implications for research

We summarised the research recommendations extracted from the "implications for research" sections of the reviews into categories of future research themes as shown in Box 2.

For each NCD grouping and nutritional risk factor, we presented the number of reviews highlighting a future research theme (e.g. the number of reviews that recommended studies with better quality for the NCD grouping cancer). We presented these data in graphs for each NCD grouping and nutrition-related risk factor.

Summarising Research Gaps

We also identified research gaps from "implications for research" section text and summarised the key specific EPICOT+ Framework components (with exceptions to the evidence and burden of disease) for which future research should address: population (e.g. gender, age, disease stage), interventions (specific intervention components, modality of intervention administration), comparison (e.g. placebo, standard care or other treatment), outcomes (e.g. adverse events, efficacy, mortality), study design (e.g. RCTs, systematic reviews, quality of study, adherence to guidelines) and time frame (duration of study, length of follow up). We presented these research gaps in tables for each NCD grouping and nutrition-related risk factor.

Box 2: Categories of future research themes for Implications for research

- no more trials required,
- more trials required overall,
- more studies with better quality required,
- more studies in a different setting required,
- more studies in a different population required,
- more studies with different interventions required,
- more studies with different outcomes required,
- more studies with longer duration of follow up required,
- further evidence unlikely to come from trials,
- more systematic reviews required,
- more cohort studies required,
- more qualitative studies required
- More cost effectives / economic evaluation studies required.

Reporting of COI, funding sources and author-financial sponsor ties

Selection of primary studies included in Cochrane nutrition reviews addressing alternative nutrition supplements.

From the eligible Cochrane nutrition reviews addressing the four major groups of NCDs and their nutrition related risk factors, we identified and selected reviews addressing alternative nutrition supplements. We selected studies on alternative nutrition supplements since they are likely to be funded by the manufacturers of such supplements, as demonstrated by the findings of a review assessing the effectives of Pine bark (*Pinus* spp.) extract for treating chronic disorders, in which Horphag Research, the manufacturer and holder of the Pycnogenol® registered trademark (Pine bark (*Pinus* spp.) extract), funded nine of the studies included in this review (38). We defined an alternative nutrition supplement as a supplement not

containing macronutrients or micronutrients but any alternative bioactive substance(s) (e.g. chitosan, cinnamon, coenzyme Q, garlic, isoflavones and creatine). We then extracted the citations of the included primary studies from the reference list of each eligible review and obtained the full-texts of these primary studies. We included full-text primary studies and theses by students and excluded abstracts, as well as primary studies in a language other than English. If there was more than one reference for the same study in a review, the most recent reference for that study was selected.

Data Collection

Data extraction for all primary studies was performed by one researcher (SR) using a standardised and piloted data extraction form. For quality control, MV, SD and CN independently checked the data from 20% of the primary studies. There was good agreement between authors. Discrepancies were resolved through discussion.

Primary studies and funding

We analysed the full-texts of English primary studies included in the selected Cochrane nutrition reviews addressing the four major NCDs and alternative nutrition supplements. We extracted the declaration of COI, disclosure of funding sources, type of funding sources, disclosure of author-sponsor financial ties and the types of author-sponsor financial ties. Declaration of COI, disclosure of funding sources and disclosure of author-sponsor financial ties were extracted from the declaration of sources of support or acknowledgments or footnotes in the article or supplementary material. Disclosed funding sources and author-sponsor financial ties were categorised as shown in Box 3 and Box 4, respectively. We also extracted author's conclusions about the effectiveness of the alternative supplement from the abstract and discussion section of the primary studies which disclosed financial sponsors or author sponsor financial ties.

Box 3: Categories of funding sources for included primary studies

Funding sources were categorised as follows:

Industry Sponsors

- Food industry (Big food, food industry-primary producer, food processing industry, wholesale and retail industry and catering industry);
- Pharmaceutical industry (Pharmaceutical and/or medical device industry),
- Mixed funding sources with food industry (Multiple funding sources for a project that include food industry e.g. a study sponsored by Big food and a governmental agency);
- Mixed funding sources with pharmaceutical industry (Multiple funding sources that include pharmaceutical industry e.g. a study sponsored by pharmaceutical industry and an academic institution);
- Mixed funding sources with food and pharmaceutical (multiple funding sources that include both pharmaceutical and food companies);

Non-industry Sponsors

- Governmental funding (Governmental agencies or structures and or inter-governmental agencies only);
- Nonprofit (Academic institutions, university affiliated research centres, non-university research institutes / research bodies, professional associations and / or non-profit entities non-industry, or both);
- Other for profit entities (Trade associations , national and international business associations and or peak bodies);
- Mixed funding sources without industry (Multiple funding sources but none belongs to food Industry or pharmaceutical industry e.g. a study is funded by an academic institution and a governmental agency).

Box 4: Categories of Author-sponsor financial ties for included primary studies.

Author-financial sponsors were defined as authors

- being a current or former industry consultant,
- being a current or former industry board members,
- being a current or former industry employees,
- receiving industry grants,
- receiving non-industry grants,
- receiving royalties,
- receiving travel reimbursement,
- receiving payment for lectures,
- receiving payment for manuscript preparation,
- receiving payment for education,
- having stocks in industry,
- having other relationships with industry,
- holding patents (planned, pending, or issued)
- Providing expert testimony.

Data Analysis

We used descriptive statistics and data are presented as counts and percentages, and visually, using tables. We calculated the Fischer exact test with a significance of $p< 0.05$, to explore the influence of funding sources and author-sponsor financial ties on author conclusions for included primary studies.

Reporting of COI, funding sources and author-sponsor financial ties

The following data from included primary studies were presented as counts and percentages of the total number of included primary studies: reporting of conflict of interest (number of studies that declared COI / total number of included primary studies), disclosure of author-financial sponsor ties (number of studies where authors disclosed author-sponsor financial ties/ total number of included primary studies) and type of study sponsor (e.g. number of studies that received funding from government/ total number of studies that disclosed funding sources).

Influence of funding source and author-financial sponsor ties on author's conclusions

We categorised sponsors into two types: industry sponsors (food industry, pharmaceutical industry, mixed funding with food, mixed funding with pharmaceutical industry , mixed funding with both industry and pharmaceutical industry and industry author-financial sponsor ties) and non-industry sponsors (governmental, non-profit, other for-profit entities, mixed funding sources without food and pharmaceutical industry and non-industry author-financial sponsor ties).

Authors' conclusions were classified as favourable or unfavourable to sponsor. Author conclusions favourable to sponsor was where the authors arrived at a positive conclusion regarding the experimental item (intervention) such that the conclusions were in favour of the sponsor. Authors' conclusions unfavourable to sponsor was where the authors arrived at a negative conclusion about the experimental item such that the conclusions were not in favour with the sponsor. We performed the Fisher exact test at a significance level of $p < 0.05$ to establish whether sponsors (industry sponsors compared with non-industry sponsors) influence author conclusions.

Ethical Considerations

The samples in this research are not people, but published reviews and primary studies, thus ethics approval is not required.

Results

Characteristics of Included Reviews

Of the 470 nutrition reviews screened, we identified 98 that addressed the four major NCDs (n=83) and their associated nutrition-related risk factors (n=15) (Figure 1). The reviews were categorised into the following NCD groupings and risk factors: cancer 15/98 (15.3 %)(31,32,39–51), chronic respiratory diseases 11/98 (11.2%)(30,52–61), cardiovascular diseases 40/98 (40.8%)(10,12,13,35,36,62–96), diabetes 17/98 (17.3%)(11,97–112), overweight and obesity 12/98 (12.2%)(33,34,37,113–121), healthy diets 3/98(3.1%)(122–124). Table 2 below provides a summary of the characteristics of these reviews. Detailed characteristics of these reviews for each NCD grouping are tabulated in the Additional File (Tables a1 to a6).

Figure 1: Selection of Cochrane nutrition reviews addressing the four major NCDs and their associated risk factors and included primary studies addressing alternative nutrition supplements.

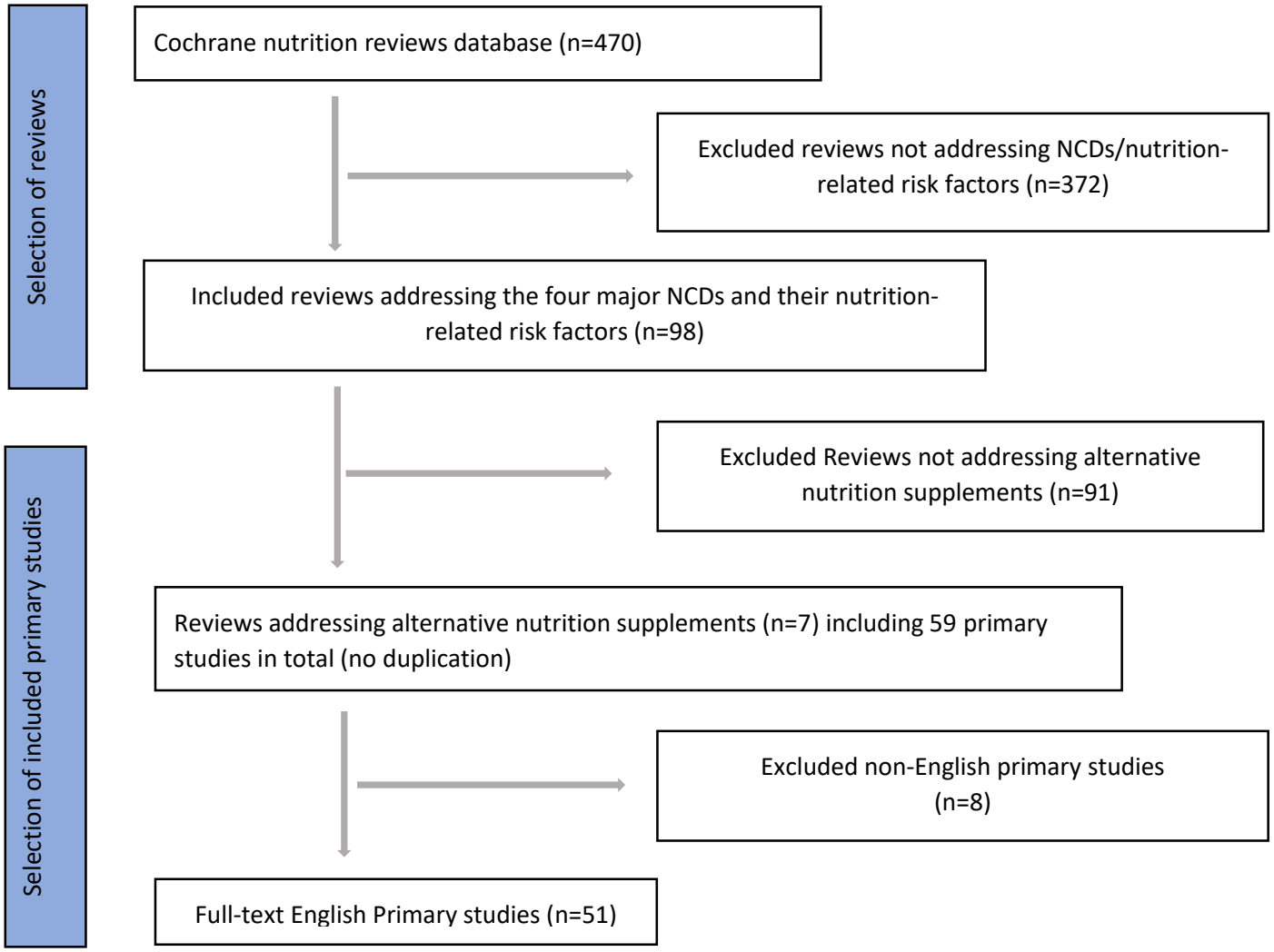


Figure 1 shows the selection of Cochrane nutrition reviews (n=98) addressing the four major NCDs (cancer, cardiovascular diseases, chronic respiratory diseases and diabetes) and their nutrition-related risk factors (obesity and overweight); and Healthy diets) and the selection of primary studies (n=51) included Cochrane nutrition reviews addressing the four major NCDs and their nutrition-related risk factors and alternative nutrition supplements

Table 2: Summary of characteristics of included Cochrane nutrition reviews addressing the four major NCDs and their nutrition-related risk factors

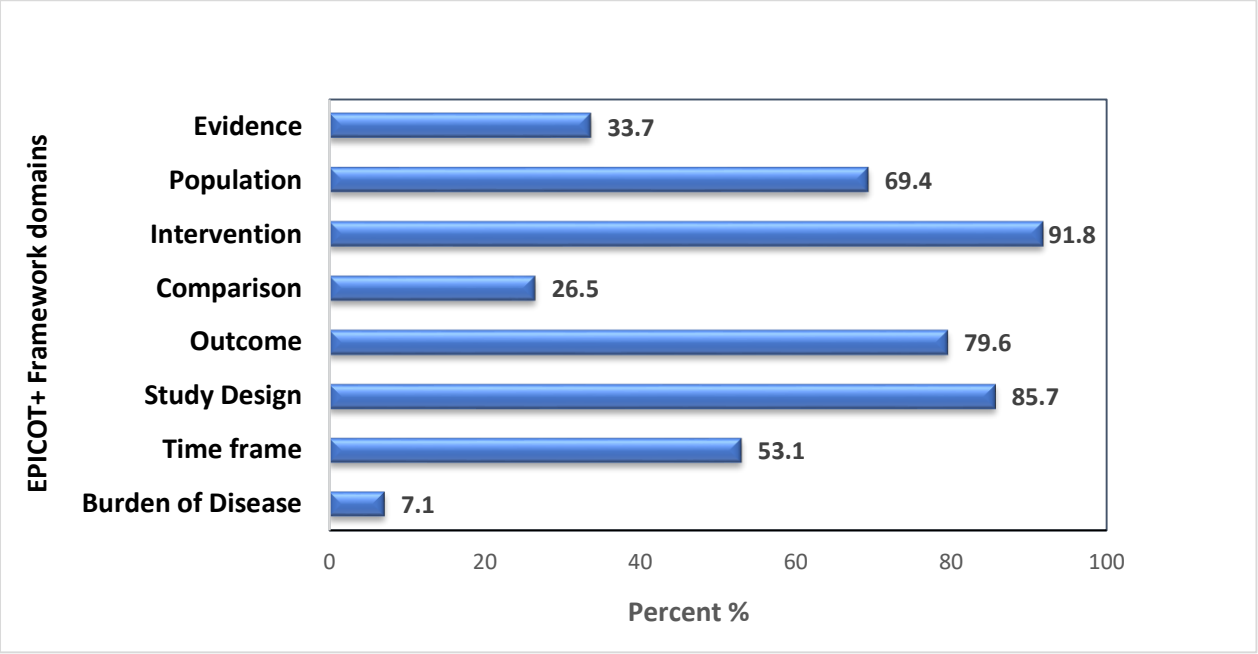
NCD Grouping N=98	Number of reviews n/N (%)	Population	Intervention	(n=)-Years published
Cancer	15/98 (15.3%)	**Healthy people (n=3):** e.g. adults ≥ 18 years (39) **People at high risk (n=4):** e.g. high risk of gastrointestinal cancer (31,39–41) **People with disease (n=8)**: e.g. Children and young people (ages≤ 21 years) with malignant disease(41–45,47,49,50)	**Consumption of specific nutrients or foods (n=6):** e.g. dietary fibre, green tea (32,39,40,43,44,49) **Diets and dietary patterns (n=1):** e.g. low bacterial diets (47) **Nutritional support (n=2):** e.g. enteral feeding (42,45) **Supplementation (n=6):** e.g. antioxidants, Vitamin C, Vitamin D (31,41,46,48,50,51)	**(n=1)**- 2006, 2007, 2011, 2012, 2013, 2014, 2015, 2018, 2020 **(n=2)**- 2008, 2016, 2017
Cardiovascular diseases	40/98 (40.8%)	**Healthy people (n=6):** e.g. adults ≥ 18 years without cardiovascular disease (69,76,82,91–93) **People at high risk (n=13):** e.g. Adults ≥18 years with essential hypertension at any risk (12,13,35,71–73,84,85,87,94,125) **People with disease (n=21):** e.g. Adults ≥18 years with existing cardiovascular disease (36,62–68,70,74,75,77–81,83,86,88–90)	**Consumption of specific food groups or foods (n=7):** whole grain cereals, cocoa powder, green or black tea (36,62,82,85,87,90,94) **Dietary patterns or dietary changes (n=15):** e.g. Mediterranean diet (12,13,35,63,64,68,70,73,75,76,81,86,91,93,125) **Supplementation (n=15):** zinc, creatine, Coenzyme Q10(65–67,72,74,77–80,83,89,92,95)	**(n=1)**-1998, 2003, 2004, 2007, 2009, 2015, 2016, 2018, 2019 **(n=2)**- 2020 **(n=4)**-2011, 2012, 2014, 2017 **(n=5)**-2006 **(n=8)**-2013
Chronic respiratory diseases	11/98 (11.2%)	**People at high risk (n=1):** e.g. Children at high risk of developing atopy or asthma (61) **People with disease (n=10):** e.g. Individuals with allergic asthma (e.g. sensitivity to aspirin or tartrazine) (30,52–56,56–58,60)	**Consumption of specific food groups or foods (n=4):** e.g. Caffeine or coffee, selenium, tartrazine (55,58,60,61) **Supplementation (n=3):** e.g. Vitamin C (53,56,59) **Dietary patterns or dietary changes (n=4):** e.g. dietary calorie reduction (30,52,54,57)	**(n=1)**- 2000, 2001, 2003, 2004, 2009, 2010, 2011, 2013, 2014 **(n=2)**- 2012
Diabetes	17/98 (17.3%)	**People at high risk (n=3):** e.g. pre-diabetic individuals, or Individuals with insulin resistance (98,104,105) **People with disease (n=14)**: e.g. Adults with diabetic retinopathy, diabetic retinopathy, diabetes kidney disease, individuals with type 1 or type 2 diabetes (11,97,99–103,106–112)	**Consumption of specific food groups or foods (n=3):** e.g. whole grain foods cinnamon (105,108,111) **Supplementation (n=4):** e.g. vitamin C/super oxidase dismutase (99,104,107,112) **Dietary patterns or dietary changes (n=8):** e.g. low glycaemic index (GI) or low glycaemic load diet (11,97,98,100–102,106,109) **Nutrition education and counselling programmes (n=2):** e.g. individual patient education for managing type 2 diabetes (103,110)	**(n=1)**-2005, 2010 **(n=2)**-2007, 2009, 2012, 2013, 2015, 2017 **(n=3)**- 2008

Obesity and overweight	12/98 (12.9%)	**People at high risk (n=1):** e.g. overweight or obese children (37) **People with disease (n=11)**: e.g overweight and obese individuals (children and adolescents ages 0 to 18 years and adults ages≥ 18 years) (33,34,113–121)	**Consumption of specific food groups or foods (n=2):** e.g. Green tea; chitosan (34,116) **Dietary patterns or dietary changes (n=5): e.g.** low glycaemic index or low glycaemic load diet (113,117,119–121) **Nutritional products and nutrients and bioactive non-nutrients (n=1)**: Chromium picolinate (CrP)(118), **Nutrition education and counselling programmes (n=4):** e.g. intervention directed at the healthcare professional or organisation of care to help implement weight reduction interventions in children and adults with overweight or obesity (33,37,114,115)	**(n=1)**-2007, 2008, 2013, 2014, 2016, 2018, 2019 **(n=2)** 2012 **(n=3)** 2017
Healthy Diets	3/98 (3.0%)	**Healthy individuals (n=3):** e.g. children ages≤ five years, Individuals ages ≤18 years, People of all ages(122–124)	**Consumption of specific food groups or foods (n=1):** e.g. fruits and vegetables (123) **Nutrition education and counselling programmes (n=1):** e.g. dietary advice and counselling interventions (124) **Policy or system programmes (n=1):** e.g. policy interventions to instigate healthy behavior change (122)	**(n=1)** 2008, 2013, 2020

Reporting of the "implications for research" section of Cochrane nutrition reviews according to the EPICOT+ framework

Figure 2 shows the extent of reporting of EPICOT+ Framework items in the "implications for research" section of Cochrane nutrition reviews addressing the four major NCDs (cancer, cardiovascular diseases, chronic respiratory diseases and diabetes) and their nutrition-related risk factors (obesity and overweight and healthy diets) (n=98). The most reported EPICOT+ item was the intervention 90/98 (91.8%). The least reported items were the evidence and the burden of disease, which were reported in 34/98 (33.7%) and 7/98 (7.1 %) of the reviews, respectively. The population was reported in 68/98 (69.4%) of reviews, the comparison in 26/98 (26.5%), the outcome in 78/98) (79.6%), the study design in 85/98 (85.7%), and the time frame in 52/98 (53.1 %). No review reported all the EPICOT+ items.

Figure 2: Percentages of included Cochrane nutrition reviews (n=98) that reported elements of the EPICOT+ framework in their "implications for research" section

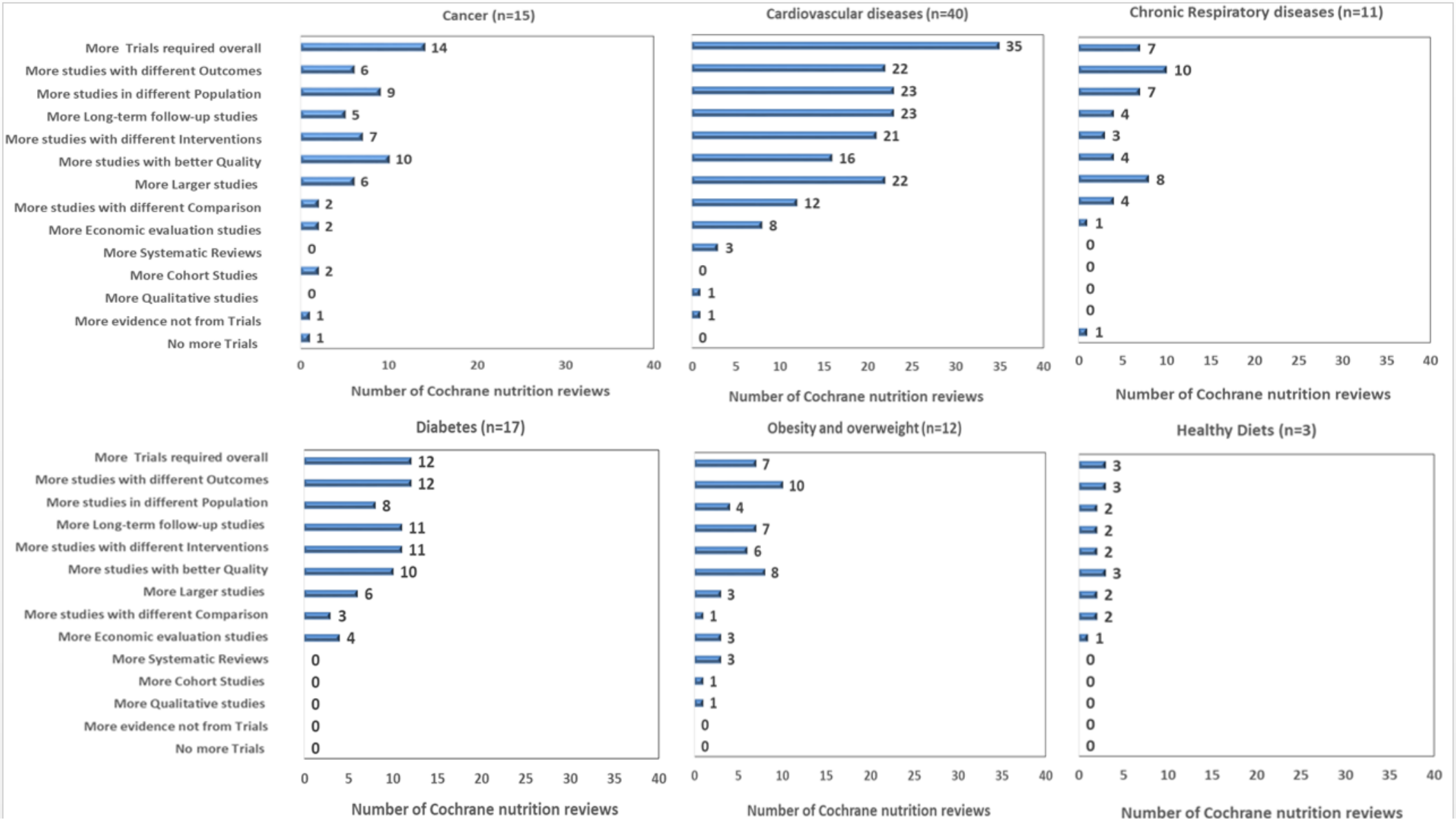


Summarising research gaps in primary research based on the "implications for research" section of Cochrane nutrition reviews

Implications for research for nutrition and the four major NCDs and the nutrition related risk factors

Figure 3 shows the future research recommendation themes extracted from the "implications for research" section of eligible Cochrane nutrition reviews for each NCD grouping and nutrition-related risk factor. Reviews in all the NCD groupings highlighted the need for more trials overall, more studies in a different population, more studies with different interventions and outcomes, more studies with larger samples and more studies with better quality. Lesser highlighted themes were more trials with a different comparison, more trials with longer follow up and more economic evaluation studies. Future research with study designs other than trials were highlighted in a few NCD groupings; more cohort studies (cancer and obesity and overweight), more systematic reviews (obesity and overweight) and more qualitative studies (cardiovascular diseases and obesity and overweight). In the chronic respiratory review, "caffeine for asthma", caffeine was found to have bronchodilatory effects. However, no more trials are required in the future since caffeine is not recognised as a treatment for asthma.

Figure 3: Implications for research for Cochrane nutrition reviews addressing the four major NCDs and their nutrition related risk factors



Research Gaps in nutrition and NCDs and nutrition related risk factors

We provide a brief summary of research gaps for each NCD grouping below. The detailed summary of the research gaps for each NCD grouping are presented in Additional Files (Section 8, Tables a9 to a14).

Research gaps for Cancer

Future studies should include homogenous study populations in terms of anticancer treatment and disease stage (47), people at high risk of cancer (e.g. younger persons, men, and in people with low vitamin D status) (31)and specific ethnic groups e.g. groups other than the Chinese population (44), as well as individuals with cancer (e.g. head and neck cancer(42), children with high-risk neuroblastoma (41)). Recommended interventions include foods containing dietary flavonoids (32) or calcium (39), consumption of green tea (40) or supplements (e.g. lycopene (51), selenium (50)). Outcomes recommended included survival (41,43,44), cancer diagnosis (e.g. liver cancer and melanoma) (46,51), quality of life (31,41), risk-benefit balance (39), safety (45) and adverse events (41,51). RCTs should adopt standard reporting guidelines.(e.g. SPIRIT; CONSORT) when planning, executing and reporting trials (31,43,44,126,127).

Research Gaps for cardiovascular

Future studies should include individuals with a high risk of cardiovascular diseases (e.g. populations with low calcium intake, elderly stroke patients), individuals with cardiovascular diseases (e.g. Hypertension (90) (77,78,85,88) (73), peripheral arterial disease (PAD) (63), familial hypercholesterolaemia (FH) (70) and acute chronic obstructive pulmonary disease (COPD) (66) or specific ethnic groups (e.g. Asian hypercholesterolaemic populations) (75) (69) (36). Recommended interventions include foods e.g. milk (87), Dietary fish (72) or Black and green tea (94)), dietary patterns (e.g. whole grain diets (82), low GI diets (76)) or supplements (e.g. selenium supplements (92), CoQ10 (89,96) and calcium supplementation (76) (94)), nutritional education and counselling programmes e.g. low sodium dietary advice and reduced sodium advice (73) and policy e.g. effects

of legislation (to alter fat contents of foods, improved labelling, pricing initiatives and improved availability of healthier (12). Outcomes recommended included cardiovascular morbidity (12,65,72,73,75,82,85,88,91) and mortality (73,85,88,91,91), blood pressure (72,77,81,91,95), hormonal and lipid outcomes (91) (72,92), health related quality of life (HRQoL) (35,66,74,96) (64), and adverse events (74,85,88,95,96). These studies should be conducted in low and middle-income countries (69), primary care and the workplace compared with hospital settings (68), population and community level (35), United Kingdom healthcare and other settings (35), lower and higher income countries (72), low and middle-income countries (69), developing countries (69), population level (e.g. workplace, institutional, regulatory) (91) and international setting(36)

***Research gaps for chronic respiratory diseases**:*

Future studies should include children (from birth) (57,59,60), adolescents (57) and adults with different types of asthma (e.g. chronic (52), exercise induced and well-controlled asthma (54,56), patients with different levels of asthma severity (58) and habitual consumers and non-consumers of coffee (58). Recommended interventions included specific foods containing caffeine (58) or omega-3 Poly-unsaturated fatty acids (omega-3 PUFAs) (54) or dietary patterns (e.g. reduced calorie intake(52), dietary sodium manipulation (54)). Outcomes recommended included clinical outcome measures (e.g. lung function, asthma symptom scores, bronchoconstriction(56,58)), exercise tolerance (56), quality of life (30,52,56–59), adverse effects (56,57,59), the impact on work and school (56) and hospital utilisation (30,57). These studies should be conducted in low-income countries such as Africa (57).

Research Gaps for Diabetes

Future studies should include people who are overweight or pre-diabetic (defined as an impaired fasting glucose or moderately elevated HbA1c), young children with diabetes (106,108), adults with type 1 and 2 diabetes (110) (102,111) (97,107,109), with and without complications (e.g. diabetic kidney disease, diabetic neuropathy) (11) (112) or individuals with normal blood pressure (11).

Recommended interventions include food groups or foods such as whole grains (105), sweet potato (111) or those containing omega-3 PUFA (99), and cinnamon) (108), dietary patterns (e.g. low glycaemic index diets (106), sustained salt reduction (11)), supplements (e.g. vitamin B) (112) or nutritional education and counselling programmes e.g. **i**mpact of individual diabetes patient education (103). Outcomes recommended included the incidence of type 2 diabetes mellitus (104), all-cause mortality (102,104), glomerular filtration rate (97), cardiovascular diseases outcomes (left ventricular function and pulse wave) and blood lipid profiles (97), weight loss, quality of life (97,100–102,104,106), validated measures of cognitive function (100), mood, depression and other aspects of functional status (110).

Research gaps for obesity and overweight

Future studies should include obese and overweight individuals (children from birth to 12 years) (37), adolescents and adults, parents in paediatric obesity interventions(121) and healthcare professionals (33). Recommended interventions include, dietary patterns (e.g. diet and physical activity, dietary and other behavioural interventions) (117) (119), nutrition education and counselling programmes (e.g. educational interventions other than brief face-to-face meetings such as weight management using e-health systems) (33) (113) (115)or whole foods (e.g chitosan) (34). Outcomes to be assessed include morbidity (34,118), mortality (34), obesity-related comorbidities (e.g. type 2 diabetes and cardiovascular disease) (120), quality of life (34,113,116,120,121) (115) or adverse effects(113,116,119,121). Trials should be reported according to standard reporting guidelines(127) (33,116).

Research gaps for healthy diets

Future studies should include people from culturally diverse backgrounds (123) and children aged five years and under (123). Recommended interventions included behavioural interventions delivered by health professionals (123), telephone or computer-based programmes, or mobile phones (123), and interventions delivered through preschools, play-groups, sports clubs, or co-

operatives (123). Outcomes included adverse effects (e.g. increased family grocery costs, adverse effects on parent self-esteem or sense of competence) (123), use of tools validated to measure outcomes (such as sun protection habits, alcohol use, smoking status, frequency of healthy eating) (122) and perspectives from health professionals and clients about the interventions (124). These studies should be conducted in low-income (123), minority or indigenous communities (123), health services (123) and sports settings (122).

Characteristics of primary studies included in Cochrane nutrition reviews addressing alternative nutrition supplements

From the eligible NCD Cochrane nutrition reviews (n=98), we identified seven eligible reviews addressing alternative nutrition supplements (32,34,83,85,89,96,108). These reviews had a combined total of 59 included primary studies (no duplicates). We excluded eight non-English studies. The list of non-English primary studies which were excluded is presented in Additional Files (Table a8). A total of 51 primary studies were included in the analysis of reporting of COI, sponsors and author financial ties and their influence on study outcomes and authors conclusions.

Table 3 below provides a brief summary of the characteristics of included primary studies. Studies addressing cancer, diabetes, and overweight and obesity all assessed a single alternative nutrition supplement, namely dietary flavonoids (128–135), cinnamon (136–145) and chitosan (146–159), respectively. Three alternative nutrition supplements (Coenzyme Q10 (160–172), creatine and creatine analogues (173–177) and garlic (178)) were assessed by studies addressing cardiovascular diseases. Forty-one primary studies were parallel randomised controlled trials and most primary studies addressing cancer were cohort studies (n=5) (128,131–133,135) and case-control studies (n=2) (129,134). A total of five of the 51 primary studies were conducted in four LMICs (Iran (166), Pakistan (141,142), India (162) and Thailand (144)) and none were conducted in Africa. The detailed characteristics of each individual included primary study is presented in Additional Files (Table a7) including: NCDs or nutrition-related risk factors and the population, interventions, comparison and

outcomes addressed, study design of primary study, the reporting of COI, funding sources and author-sponsor financial ties, the authors conclusion (favourable or unfavourable to sponsor and author-financial sponsor ties) and the country where the primary study was conducted..

Table 3: Summary of characteristics of included primary studies

NCD Grouping	Alternative Nutrition Supplement assessed (n studies)	Population addressed	Study Design	Country of study
Cancer	Dietary Flavonoids **(n=8)** (128–135)	Adults of any age with or without colorectal cancer and/or adenomas.	Cohort **(n=5)** (129,131–133,135) Case control **(n=2)** (128,134) Parallel RCTs **(n=1)** (130)	USA **(n=4)** Japan **(n=2)** Scotland **(n=1)** Netherlands **(n=1)**
Cardiovascular diseases	Coenzyme Q10 **(n=13)** (160–172)	Patients with chronic heart failure (with reduced ejection fraction (HFREF) or normal ejection fraction (HFNEF), participants with chronic heart failure of any severity, Chronic heart failure with leA-sided and right-sided heart failure.	Parallel RCTs **(n=16)** (160,161,163–168,170–174,177,178) Cross over RCTs **(n=2)** (169,179) Non RCTs **(n=1)** (162)	USA **(n=1)** Italy **(n=4)** Iran **(n=1)** India **(n=1)** Israel **(n=1)** Japan **(n=2)** Russia **(n=1)** Finland **(n=1)** Sweden **(n=1)** Germany **(n=2)** Denmark **(n=1)** Australia **(n=1)** New Zealand **(n=1)** South Korea **(n=1)**
	Creatine and Creatine analogues **(n=5)** (173–177)	Adults >18 years of age with cardiovascular disease (essential hypertension, heart failure or myocardial infarction)		
	Garlic **(n=1)** (178)	Adults ≥ 18 years of age, with primary hypertension (systolic blood pressure > 140 mmHg and/or a diastolic blood pressure of > 90mmHg)		
Diabetes	Cinnamon **(n=10)** (136–145)	People with either type 1 or type 2 diabetes mellitus diagnosed using the standard criteria valid at the time of the beginning of the trial.	Parallel RCTs **(n=10)** (136–145)	UK **(n=1)** USA **(n=4)** Pakistan **(n=2)** Thailand **(n=1)** Germany **(n=1)** Netherlands **(n=1)**

Obesity and overweight	Chitosan **(n=14)** (147–159)	Adults >18 years and older defined as overweight or obese at baseline using body mass index (BMI) cut points and percentage excess weight compared with ideal weight/height tables.	Parallel RCTs **(n=14)** (146–159)	Finland **(n=1)** UK **(n=2)** Canada **(n=1)** USA **(n=2)** Singapore **(n=1)** Italy **(n=6)** New Zealand **(n=1)**

Reporting of conflicts of interest, funding sources and author-sponsor financial ties

Table 4 summarises the reporting of COI, funding sources and of the author-sponsor financial ties in full-text English primary studies primary studies (n=51) included in Cochrane nutrition reviews addressing alternative nutrition supplements and the four major NCDs (cancer, cardiovascular diseases, chronic respiratory diseases and diabetes) and their nutrition-related risk factor (obesity and overweight). The author-sponsor financial ties are classified according to whether the sponsors are industry or non-industry related.

Of the 51 full-text English primary studies included in Cochrane nutrition reviews addressing alternative nutrition supplements, 10/51 (19.6%) reported their conflicts of interest (128–130,132,135,137,140,146,160,171). Of these, eight reported no COI (128–130,132,135,137,140,171) and two reported having existing conflict of interest. Of the two studies with existing COI, one author reported being the president of the company NxCare Inc., which manufactured and provided the alternative supplement chitosan (Calorie-care) (146) and the authors of the other study reported having conflict of interest with the company (Kaneka Co.) (160).

Funding sources were disclosed in 27/51 (52.9%) studies (Table 4), of which 11 reported industry sponsors and 16 reported non-industry sponsors. Of those studies reporting industry sponsors, seven reported pharmaceutical industry sponsor s(e.g. Marshtech Ltd, London; Vanson inc.) (143,146,155,157,160,164,180), and four reported mixed funding sources including the pharmaceutical industry (e.g. Trippler Army Medical Center, Integrity Nutreceuticals International and US Department of Agriculture) (136,137,158,170). Of those studies reporting non-industry sponsors, eight reported government sponsors (e.g. National Center for Research Resources, National Center for Research Resources and National Institutes of Health) (128–130,132,134,139,140,165), five reported mixed funding sources excluding food and pharmaceutical industry (e.g. Swedish Medical Research Council (4494 and 9515), the Swedish Heart and Lung Foundation and the Salus 60-year Medical Foundation) (131,133,135,138,174), and three reported non-profit sponsors (e.g. University Grants Commission/NWFP Agricultural University, Peshawar,

Pakistan) (142,167,172). None of the studies received funding from the food industry alone, mixed funding sources including the food Industry, mixed funding sources including the pharmaceutical and food industries, or from other for-profit entities.

Author-sponsor financial ties were disclosed in 9/51 (17.6%) studies. Of these, one study reported that one author was an industry employee (146) and the remaining studies reported that authors received non-industry grants, fellowships or awards (128,129,132,134–136,155,158). Author-sponsor financial ties were reported separately from the conflicts of interest.

Table 4: Reporting of conflicts of interest, funding sources and author-sponsor financial ties in primary studies (n=51)

Domain	n/N (%)
COI disclosed	10/51 (19.6)
Existing COI	2/10 (20)
None	8/10 (80)
Funding sources disclosed	27/51 (52.9)
Industry Sponsors	11/27 (40.7)
• Pharmaceutical	7/27 (25.9)
• Mixed funding sources with pharmaceutical industry	4/27 (14.8)
Non-industry Sponsors	16/27 (59.2)
• Government	8/27 (29.6)
• Mixed funding sources without pharmaceutical and food industry	5/27 (18.5)
• Non-Profit	3/27 (11.1)
Author-sponsor financial ties disclosed	9/51 (17.6)
Industry author-sponsor financial ties	
• Current or former employee of Pharmaceutical industry	1/9 (11.1)
Non-industry author-sponsor financial ties	
• Non-industry grants	8/9 (88.8)

Author conclusions

Of the 11 studies which received industry funding, seven studies had favourable author conclusions (137,143,146,157,160,164,180) and four had unfavourable author conclusions (136,155,158,170). Of the 16 studies which received non-industry funding, eight had favourable (128,130,131,134,140,141,167,174) and eight had unfavourable author conclusions (128,132,133,135,138,139,165,172). One study with industry author-financial sponsor ties had favourable author conclusions (146) and of the eight studies with non-industry author-financial sponsor ties , one had favourable author conclusion (129) and seven had unfavourable author conclusions (128,132,134–136,155,158).

Influence of funding source on author's conclusions in included primary studies

Table 5 shows the association between author conclusions with funding sources and author-sponsor financial ties in included primary studies that reported funding sources (n=36). Of the 27 studies that reported funding sources, and nine studies that reported author-sponsor financial ties, 12 studies reported having industry-related funding sources and author-sponsor financial ties and 24 studies had non-industry funding sources and author-sponsor financial ties (Table 5). Of the 12 studies which reported having industry sponsors and author-sponsor financial ties, eight had favourable and four had unfavourable author conclusions. Of the 24 studies with non-industry funding sources and author-financial sponsor ties, eight studies had favourable and eight had unfavourable author conclusions.

We found no evidence of an association between authors making favourable conclusions and having industry sponsors and author-financial sponsors (8/12) compared with having non-industry sponsors and author-financial sponsors ties (10/24) (Fisher exact test, p = 0.289).

Table 5: Associations between author conclusions with sponsor and author-sponsor financial ties in primary studies

Primary study results	**Funding sources and author-financial sponsor ties**			
Author conclusions	Total	Industry	Non-industry	Fisher Exact test p value
	36	12	14	p= 0.289
Favourable	18	8	10	
Unfavourable	18	4	14	

Discussion

Reporting of "implications for research" section according to EPICOT+ framework

In 98 Cochrane nutrition reviews addressing the four major NCDs (cancer, cardiovascular diseases, chronic respiratory diseases and diabetes), nutrition-related risk factor (obesity) and healthy diets, we found that the most reported EPICOT+ items were the intervention, study design, outcomes, population and the timeframe and the lesser reported items were the comparison, the evidence and the burden of disease. These findings are consistent with findings in a similar previous bibliometric analysis of Cochrane HIV reviews, where the most reported EPICOT+ framework elements in the "implications for research" section were the population, intervention, outcome and time frame, and the lesser reported elements were the evidence, comparison and burden of diseases (181). According to Brown et.al, unlike the evidence, population, intervention, comparison and outcome, reporting the burden of disease in the "implications for research" section is optional (20). This maybe the cause of the lesser reporting of the burden of disease seen in our study. Considering the burden of disease when formulating research recommendations is important as this will inform researchers and policy makers of the settings for which urgent research is needed. Mbuagbaw et.al hypothesized that the lack of reporting of the evidence item may be explained by the fact that authors allude to the evidence in the in the meta analyses and they might find it repetitive to do the same in the "implications for research" section (181). In addition, some of the included reviews in our analysis presented the results of their meta-analyses as 'Summary of Findings tables', where the certainty of evidence for the main outcomes of each review is evaluated by review authors using the GRADE certainty framework. This has become a prerequisite for conducting Cochrane systematic reviews according to the Cochrane Handbook (16).

Summarising research gaps in primary research based on the "implications for research" section of Cochrane nutrition reviews

Implications for research

From analysing the "implications for research" section of 98 Cochrane nutrition reviews addressing the four major NCDs and their nutrition-related risk factors, our findings suggest the need for more RCTs, more studies with different populations, interventions, outcomes and larger studies in all NCD groupings. Our results are comparable with findings in a similar study in Cochrane reviews addressing HIV which suggested the need for more RCTs overall, more studies with different outcomes and more studies with different interventions (181). Recommendations for future studies with a design other than randomised control trials (cohort studies, qualitative studies and Systematic reviews) were highlighted in very few studies for cancer, chronic respiratory diseases and obesity and overweight. More future studies with longer duration of follow up were highlighted for all NCD groupings, however studies of longer duration may be done as much as resources allow.

Research Gaps

We identified specific research gap areas (population, intentions, comparison, outcomes and study design) in the evidence base of nutrition and the four major NCDs and their nutrition-related risk factors for which future research should address. The research gaps identified in Cochrane nutrition reviews across all NCDs and nutrition-related risk factors pointed to issues relating to quality of studies, settings in which studies are to be conducted and the execution and reporting of studies. The need was identified for future trials to minimise risk of bias by implementing proper methods of randomisation, allocation concealment and blinding, ITT or PP analyses and explicitly describing these methods when reporting trials. More research in LMICs was highlighted in reviews addressing cardiovascular diseases, chronic respiratory diseases and obesity and overweight, whilst more research in high income countries was highlighted in reviews on cardiovascular diseases.

Future researchers were recommended to adopt Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (guidelines which provide guidance on how researchers should fully describe the contents of protocols for clinical trials) (126) when conducting RCTs for cancer. To achieve standardised reporting of interventional trials in cancer, cardiovascular diseases and obesity and overweight, researchers were recommended to adopt Consolidated Standards for Reporting of Trials (CONSORT) guidelines (guidelines which provide guidance on reporting how a trial was designed, analysed, and interpreted; and the progress of all participants through the trial) (127).

Reporting of conflicts of interest, funding sources and author-sponsor financial ties

In 51 primary studies included in Cochrane nutrition reviews addressing alternative nutrition supplements and the four major NCDs and their nutrition-related risk factors, we found that conflicts of interest were not well reported. Our findings of poor reporting of COI are similar to previous studies that explored the reporting of COI in case-control and cohort studies on effects of dairy consumption and whole grain food consumption on cardiovascular outcomes and mortality, as well as in RCTs of nutritional interventions addressing obesity (182–184).

In our analysis, funding sources were reported in more than half of the included primary studies, and nearly a quarter of these were industry sponsors. The lower proportion of reported industry sponsors in our study was also found in studies exploring the influence of funding sources in primary studies addressing effects of nutrition interventions on obesity and effects of consumption of dairy products on cardiovascular outcomes and mortality (182,185). The lower proportion of reported industry sponsors might be due to the lack of disclosure of industry sponsors by primary study authors. The disclosure of author-sponsor financial ties was poor, with only 1 study reporting industry author-sponsor financial ties. These results are consistent with findings of a meta-analysis of Cochrane reviews of drug trials in which author-sponsor financial ties for included RCTs were poorly reported (186).

Influence of sponsors and author-sponsor financial ties on author conclusions in included primary studies

Based on included primary studies which reported their funding sources and author-financial sponsor ties, we found no association between authors making favourable conclusions and having industry sponsors compared with having non-industry sponsors. Our results are consistent with findings from a meta analyses of case control and cohort studies examining the effect of dairy food intake on cardiovascular disease and mortality and another meta analyses of cohort studies and reviews exploring the association of industry sponsorship with outcomes of nutrition studies, in which they found no association between industry sponsors and author conclusions(182,187)**.** . Our findings are inconsistent as well with a previous study which explored the reporting of sponsors, COI and author financial ties and their influence on study outcomes and author conclusions in systematic reviews of artificially sweetened beverages on weight outcomes (21)**.**. The differences in findings may be due to that our sample size was smaller and the association between industry author-sponsor financial ties and author conclusions may have not been dictated.

From our study and other previous studies, it is apparent that COI, sources of funding and author-sponsor financial ties is under reported. The under reporting of COI, sponsors and author-sponsor financial ties obscures a true picture of the COI where it exists. This limits the interpretation and judgement of the accuracy of research findings and the application of research findings by stakeholders (e.g. scientists, readers, policy makers, clinicians) since possible bias introduced by the sponsors and by the author relationship with sponsors is obscured. Searching online for disclosure of COI, sponsors and author-sponsor financial ties is a possibility, however it might be cumbersome and time consuming, and this is subject to whether the declarations were recorded or not online. To improve the reporting of COI, funding sources, and author-sponsor financial ties, journals are urged to include this information in abstracts of articles submitted to PubMed Central (online database for biomedical literature) (188).

Limitations

Our study has several limitations. The search for nutrition reviews addressing the four major NCDs and their nutrition-related risk factors was done up to 2015, and thus we may have missed relevant Cochrane reviews published thereafter. Although we used the most recent updates of the included reviews, our search remained limited, the research gaps we identified were restricted to those reported in Cochrane systematic reviews.

The subset of primary studies we analysed was from a non-randomised sample of Cochrane reviews addressing alternative nutrition supplements, therefore our findings are only specific to these primary studies and Cochrane reviews. In our analysis, we included full-text English primary studies only and excluded primary studies published in languages other than English. Our findings may have been different if we had included the non-English primary studies. We did not contact the authors for undisclosed COI, funding sources and author financial ties or search for these declarations online, as a result we may have missed existing COI, funding sources and author financial ties. Our classification of sponsors was done based on a simple categorisation of the type of funder only, and we did not explore the actual origin of the funding for each funder. This may have led to some misclassification, for example, one study was classified as non-industry (not for profit charity organisation) yet, the organisation is financially supported by food industries.

Conclusions

Our findings show that EPICOT+ Framework items were not well reported in the “implications for research” section in most reviews. We identified research gaps in the field of nutrition and NCDs that may be useful to researchers, funders, and policy makers when planning future research. Author-sponsor financial ties may have influenced author conclusions, however, we cannot state this with certainty since the sample analysed was small. Future studies exploring the influence of sponsors and author-sponsor financial ties on study conclusions should have larger sample sizes. The poor disclosure of COI, funding source and author-sponsor financial ties in included primary studies

warrants the need for journals and their editorial boards to urge authors to report COI, sponsors and author-financial sponsor ties, especially for studies that received industry sponsorship.

List of Abbreviations

ABI: Ankle braclial pressure index

ALA: Alpha-linolenic acid

AMSTAR 2: AMSTAR 2: Assessment of multiple systematic reviews 2

BP: Blood Pressure

BMI: Body mass index

zBM: Body mass index z-score

BNP: Brain natriuretic Peptide

CABG: coronary artery bypass grafting

CHD: Coronary heart disease

CI: Confidence interval

CoQ10: Coenzyme Q10

COI: Conflict of interest

CONSORT: Consolidated Standards for Reporting of Trials

COPD: Chronic obstructive pulmonary disease

CrP: C-reactive protein

CVD: Cardiovascular Diseases

DKD: Diabetes Kidney disease

DOI: Digital Object Identifier

EPA: Eicosapentaenoic acid

EPICOT+ Framework: Evidence, Population, Intervention, Comparison, Outcome, Timeliness, Study design and Burden of disease Framework

EuroQoL: Euro Quality of Life

EuroQol-5D: Euro Quality of Life based on 5 dimensions

FBG: Fast blood glucose

FH: Familial hypercholesterolemia

GFR: Glomerular filtrate rate

GI: Glycaemic index

HbA1c: Haemoglobin A1c

HDL: High density lipoprotein

HOMA-IR: homeostasis model assessment of insulin resistance

HRQoL: Health related Quality of Life

ITT: Intention to treat analysis

LMICs: Low to middle income countries

LeA: ventricular ejection fraction

LDL: Low density lipoprotein

MI: Myocardial infaction

MSG: Monosodium glutamate

NCD: Non-communicable Diseases

NYHA: New York Heart Association

Omega-3 PUFA: Omega -3 Poly unsaturated fatty acids

OR: Odds ratio

PAD: Peripheral arterial disease

PCI: Percutaneous Coronary Intervention

PICO: Participant, intervention, comparison. Outcome

PP: Per protocol analysis

PPARs: Peroxidase proliferator-activated receptors

PPG: Post prandial glucose

PSA: prostate-specific antigen

PTCA: percutaneous transluminal coronary angioplasty

RR: Risk ratio

RCT(s): Randomised Control Trial(s)

SARMS: selective androgen receptor modulators

SSB: sugar-sweetened beverages

SWAL-QOL: Swallowing Quality of Life Questionnaire

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

TT2DM: Type 2 diabetes mellitus

TTM SOC: Transtheoretical model stages of change

VO2: Oxygen uptake

WHO: World Health organisation

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated, used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Sheena Ruzive acknowledges financial assistance from Prof Lisa Bero, recipient of the 2015 Cochrane Anne Anderson Award, whereby a cash sum was designated by the recipient to assist a woman from a low-resource setting with Cochrane activities.

Sheena Ruzive received a bursary from Novartis SA (Pty) Ltd which was used to cover the cost of her Master of Science (Clinical Epidemiology) tuition fees.

Authors' contributions

CEN -conception and design of the work; analysis and interpretation of data; substantively revised work

SD- conception and design of the work; acquisition of data; analysis and interpretation of data and substantively revised work

MV- the acquisition; analysis and interpretation of data and substantively revised work

SR- acquisition of data, analysis and interpretation of data; drafted and revised the work

Acknowledgements

We would like to thank Michael McCaul from the Centre of Evidence base Health Care and Biostatistics and Epidemiology unit Stellenbosch University for his assistance with data analysis.

Authors' information (optional)

Not Applicable

Footnotes

Not Applicable

References

1. Ezzati M, Pearson-Stuttard J, Bennett JE, Mathers CD. Acting on non-communicable diseases in low- and middle-income tropical countries. Nature. 2018 Jul;559(7715):507–16.

2. WHO | Global Action Plan for the Prevention and Control of NCDs 2013-2020 [Internet]. WHO. [cited 2016 Jul 14]. Available from: http://www.who.int/nmh/events/ncd_action_plan/en/

3. Non communicable diseases [Internet]. [cited 2020 Oct 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

4. Wang S, Marquez P, Langenbrunner J. Toward a healthy and harmonious life in China : stemming the rising tide of non-communicable diseases [Internet]. The World Bank; 2011 Jul [cited 2016 Jul 21] p. 1–48. Report No.: 63426. Available from: http://documents.worldbank.org/curated/en/2011/07/14639951/toward-healthy-harmonious-life-china-stemming-rising-tide-non-communicable-diseases

5. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and Vegetable Consumption and Risk of Coronary Heart Disease: A Meta-Analysis of Cohort Studies. J Nutr. 2006 Jan 10;136(10):2588–93.

6. Hardy ML, Duvall K. Multivitamin/multimineral supplements for cancer prevention: implications for primary care practice. Postgrad Med. 2015 Jan 2;127(1):107–16.

7. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes, Cardiovascular Disease, and Weight Gain. J Nutr. 2012 Jan 7;142(7):1304–13.

8. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJL, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet Lond Engl. 2002 Nov 2;360(9343):1347–60.

9. Langley-Evans SC. Nutrition in early life and the programming of adult disease: a review. J Hum Nutr Diet. 2015;28(s1):1–14.

10. Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. In: Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 2015 [cited 2016 Sep 26]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011737/abstract

11. Suckling RJ, He FJ, MacGregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. Cochrane Database Syst Rev [Internet]. 2010 [cited 2020 Jul 2];(12). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006763.pub2/full

12. Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore HJ, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(5). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002137.pub3/full

13. Hartley L, Igbinedion E, Holmes J, Flowers N, Thorogood M, Clarke A, et al. Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases.

Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009874.pub2/full

14. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001 Aug 11;323(7308):334–6.

15. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996 Jan 13;312(7023):71–2.

16. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2020 Dec 28]. Available from: /handbook/current

17. Clarke L, Clarke M, Clarke T. How useful are Cochrane reviews in identifying research needs? J Health Serv Res Policy. 2007 Apr;12(2):101–3.

18. Lavis JN, Posada FB, Haines A, Osei E. Use of research to inform public policymaking. Lancet Lond Engl. 2004 Nov 30;364(9445):1615–21.

19. Mbuagbaw L, Kredo T, Welch V, Mursleen S, Ross S, Zani B, et al. Critical EPICOT items were absent in Cochrane human immunodeficiency virus systematic reviews: a bibliometric analysis. J Clin Epidemiol. 2016 Jun;74:66–72.

20. Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. BMJ. 2006 Oct 14;333(7572):804–6.

21. Mandrioli D, Kearns CE, Bero LA. Relationship between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews. PloS One. 2016;11(9):e0162198.

22. Schott G, Pachl H, Limbach U, Gundert-Remy U, Ludwig W-D, Lieb K. The financing of drug trials by pharmaceutical companies and its consequences. Part 1: a qualitative, systematic review of the literature on possible influences on the findings, protocols, and quality of drug trials. Dtsch Ärztebl Int. 2010 Apr;107(16):279–85.

23. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

24. AMSTAR - Assessing the Methodological Quality of Systematic Reviews [Internet]. [cited 2020 Dec 30]. Available from: https://amstar.ca/Amstar_Checklist.php

25. Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice. Conflict of Interest in Medical Research, Education, and Practice [Internet]. Lo B, Field MJ, editors. Washington (DC): National Academies Press (US); 2009 [cited 2020 Dec 28]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK22942/

26. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. PLOS Med. 2016 May 24;13(5):e1002028.

27. Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between Funding Source and Conclusion among Nutrition-Related Scientific Articles. PLOS Med. 2007 Jan 9;4(1):e5.

28. G S, H P, U L, U G-R, Wd L, K L. The financing of drug trials by pharmaceutical companies and its consequences. Part 1: a qualitative, systematic review of the literature on possible influences on the findings, protocols, and quality of drug trials. Dtsch Arzteblatt Int. 2010 Apr 23;107(16):279–85.

29. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA. Financial Conflicts of Interest and Reporting Bias Regarding the Association between Sugar-Sweetened Beverages and Weight Gain: A Systematic Review of Systematic Reviews. PLOS Med. 2013 Dec 31;10(12):e1001578.

30. Thien FC, Luca SD, Woods RK, Abramson MJ. Dietary marine fatty acids (fish oil) for asthma in adults and children. Cochrane Database Syst Rev [Internet]. 2000 [cited 2020 Jul 2];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001283/full

31. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Krstic G, Wetterslev J, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007469.pub2/full

32. Jin H, Leng Q, Li C. Dietary flavonoid for preventing colorectal neoplasms. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009350.pub2/full

33. Flodgren G, Gonçalves-Bradley DC, Summerbell CD. Interventions to change the behaviour of health professionals and the organisation of care to promote weight reduction in children and adults with overweight or obesity. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Dec 29];(11). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000984.pub3/full

34. Jull AB, Mhurchu CN, Bennett DA, Dunshea-Mooij CA, Rodgers A. Chitosan for overweight or obesity. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003892.pub3/full

35. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(12). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002128.pub5/full

36. Qin Y, Niu K, Zeng Y, Liu P, Yi L, Zhang T, et al. Isoflavones for hypercholesterolaemia in adults. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009518.pub2/full

37. Brown T, Moore TH, Hooper L, Gao Y, Zayegh A, Ijaz S, et al. Interventions for preventing obesity in children. Cochrane Database Syst Rev [Internet]. 2019 [cited 2020 Jul 2];(7). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001871.pub4/full

38. Robertson NU, Schoonees A, Brand A, Visser J. Pine bark (*Pinus* spp.) extract for treating chronic disorders. Cochrane Database Syst Rev [Internet]. 2020 [cited 2021 Apr 11];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008294.pub5/full

39. Weingarten MAM, Trestioreanu AZ, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003548.pub4/full

40. Filippini T, Malavolti M, Borrelli F, Izzo AA, Fairweather-Tait SJ, Horneber M, et al. Green tea (Camellia sinensis) for the prevention of cancer. Cochrane Database Syst Rev [Internet]. 2020 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005004.pub3/full

41. Peinemann F, Dalen EC van, Enk H, Berthold F. Retinoic acid postconsolidation therapy for high-risk neuroblastoma patients treated with autologous haematopoietic stem cell transplantation. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010685.pub3/full

42. Nugent B, Lewis S, O'Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007904.pub3/full

43. Dewey A, Baughan C, Dean TP, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Cochrane Database Syst Rev [Internet]. 2007 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004597.pub2/full

44. Jin X, Beguerie JR, Sze DM, Chan GC. *Ganoderma lucidum* (Reishi mushroom) for cancer treatment. Cochrane Database Syst Rev [Internet]. 2016 [cited 2020 Jul 2];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007731.pub3/full

45. Ward EJ, Henry LM, Friend AJ, Wilkins S, Phillips RS. Nutritional support in children and young people with cancer undergoing chemotherapy. Cochrane Database Syst Rev [Internet]. 2015 [cited 2020 Jul 2];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003298.pub3/full

46. Vinceti M, Filippini T, Giovane CD, Dennert G, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. Cochrane Database Syst Rev [Internet]. 2018 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005195.pub4/full

47. Dalen EC van, Mank A, Leclercq E, Mulder RL, Davies M, Kersten MJ, et al. Low bacterial diet versus control diet to prevent infection in cancer patients treated with chemotherapy causing episodes of neutropenia. Cochrane Database Syst Rev [Internet]. 2016 [cited 2020 Jul 2];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006247.pub3/full

48. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004183.pub3/full

49. Yao Y, Suo T, Andersson R, Cao Y, Wang C, Lu J, et al. Dietary fibre for the prevention of recurrent colorectal adenomas and carcinomas. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003430.pub2/full

50. Dennert G, Horneber M. Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients. Cochrane Database Syst Rev [Internet]. 2006 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005037.pub2/full

51. Ilic D, Forbes KM, Hassed C. Lycopene for the prevention of prostate cancer. Cochrane Database Syst Rev [Internet]. 2011 [cited 2020 Jul 2];(11). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008007.pub2/full

52. Cheng J, Pan T. Calorie controlled diet for chronic asthma. Cochrane Database Syst Rev [Internet]. 2003 [cited 2020 Jul 2];(2). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004674.pub2/full

53. Allam MF, Lucena RA. Selenium supplementation for asthma. Cochrane Database Syst Rev [Internet]. 2004 [cited 2020 Jul 2];(2). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003538.pub2/full

54. Pogson Z, McKeever T. Dietary sodium manipulation and asthma. Cochrane Database Syst Rev [Internet]. 2011 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000436.pub3/full

55. Ardern K. Tartrazine exclusion for allergic asthma. Cochrane Database Syst Rev [Internet]. 2001 [cited 2020 Jul 2];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000460/full

56. Wilkinson M, Hart A, Milan SJ, Sugumar K. Vitamins C and E for asthma and exercise-induced bronchoconstriction. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010749.pub2/full

57. Adeniyi FB, Young T. Weight loss interventions for chronic asthma. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(7). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009339.pub2/full

58. Welsh EJ, Bara A, Barley E, Cates CJ. Caffeine for asthma. Cochrane Database Syst Rev [Internet]. 2010 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001112.pub2/full

59. Milan SJ, Hart A, Wilkinson M. Vitamin C for asthma and exercise-induced bronchoconstriction. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(10). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010391.pub2/full

60. Zhou Y, Yang M, Dong BR. Monosodium glutamate avoidance for chronic asthma in adults and children. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004357.pub4/full

61. Maas T, Kaper J, Sheikh A, Knottnerus JA, Wesseling G, Dompeling E, et al. Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. Cochrane Database Syst Rev [Internet]. 2009 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006480.pub2/full

62. Jepson RG, Kleijnen J, Leng GC. Garlic for peripheral arterial occlusive disease. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000095.pub2/full

63. Aung PP, Maxwell H, Jepson RG, Price J, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database Syst Rev [Internet]. 2007 [cited 2020 Jul 2];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000123.pub2/full

64. Bath PM, Lee HS, Everton LF. Swallowing therapy for dysphagia in acute and subacute stroke. Cochrane Database Syst Rev [Internet]. 2018 [cited 2020 Jul 2];(10). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000323.pub3/full

65. Kleijnen J, Mackerras D. Vitamin E for intermittent claudication. Cochrane Database Syst Rev [Internet]. 1998 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000987/full

66. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(12). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000998.pub3/full

67. Wilkinson EA. Oral zinc for arterial and venous leg ulcers. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001273.pub3/full

68. Thompson RL, Summerbell CD, Hooper L, Higgins JP, Little P, Talbot D, et al. Dietary advice given by a dietitian versus other health professional or self-help resources to reduce blood cholesterol. Cochrane Database Syst Rev [Internet]. 2003 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001366/full

69. Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Smith GD. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database Syst Rev [Internet]. 2011 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001561.pub3/full

70. Malhotra A, Shafiq N, Arora A, Singh M, Kumar R, Malhotra S. Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001918.pub3/full

71. Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev [Internet]. 2009 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002091.pub2/full

72. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2020 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003177.pub5/full

73. Hooper L, Bartlett C, Smith GD, Ebrahim S. Advice to reduce dietary salt for prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2004 [cited 2020 Jul 2];(1).

Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003656.pub2/full

74. Campbell A, Price J, Hiatt WR. Omega-3 fatty acids for intermittent claudication. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(7). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003833.pub4/full

75. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(4). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004022.pub4/full

76. Clar C, Al-Khudairy L, Loveman E, Kelly SA, Hartley L, Flowers N, et al. Low glycaemic index diets for the prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(7). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004467.pub3/full

77. Dickinson HO, Nicolson D, Cook JV, Campbell F, Beyer FR, Ford GA, et al. Calcium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev [Internet]. 2006 [cited 2020 Jul 2];(2). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004639.pub2/full

78. Dickinson HO, Nicolson D, Campbell F, Cook JV, Beyer FR, Ford GA, et al. Magnesium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev [Internet]. 2006 [cited 2020 Jul 2];(3). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004640.pub2/full

79. Dickinson HO, Nicolson D, Campbell F, Beyer FR, Mason J. Potassium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev [Internet]. 2006 [cited 2020 Jul 2];(3). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004641.pub2/full

80. Beyer FR, Dickinson HO, Nicolson D, Ford GA, Mason J. Combined calcium, magnesium and potassium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev [Internet]. 2006 [cited 2020 Jul 2];(3). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004805.pub2/full

81. He FJ, Li J, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(4). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004937.pub2/full

82. Kelly SA, Hartley L, Loveman E, Colquitt JL, Jones HM, Al-Khudairy L, et al. Whole grain cereals for the primary or secondary prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(8). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005051.pub3/full

83. Horjus DL, Oudman I, Montfrans GA van, Brewster LM. Creatine and creatine analogues in hypertension and cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2011 [cited 2020 Jul 2];(11). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005184.pub2/full

84. Curioni C, André C, Veras R. Weight reduction for primary prevention of stroke in adults with overweight or obesity. Cochrane Database Syst Rev [Internet]. 2006 [cited 2020 Jul 2];(4).

Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006062.pub2/full

85. Stabler SN, Tejani AM, Huynh F, Fowkes C. Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(8). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007653.pub2/full

86. Smart NA, Marshall BJ, Daley M, Boulos E, Windus J, Baker N, et al. Low-fat diets for acquired hypercholesterolaemia. Cochrane Database Syst Rev [Internet]. 2011 [cited 2020 Jul 2];(2). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007957.pub2/full

87. Usinger L, Reimer C, Ibsen H. Fermented milk for hypertension. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(4). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008118.pub2/full

88. Semlitsch T, Jeitler K, Berghold A, Horvath K, Posch N, Poggenburg S, et al. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev [Internet]. 2016 [cited 2020 Jul 2];(3). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008274.pub3/full

89. Madmani ME, Solaiman AY, Agha KT, Madmani Y, Shahrour Y, Essali A, et al. Coenzyme Q10 for heart failure. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(6). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008684.pub2/full

90. Ried K, Fakler P, Stocks NP. Effect of cocoa on blood pressure. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(4). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008893.pub3/full

91. Adler AJ, Taylor F, Martin N, Gottlieb S, Taylor RS, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(12). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009217.pub3/full

92. Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(1). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009671.pub2/full

93. Rees K, Takeda A, Martin N, Ellis L, Wijesekara D, Vepa A, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2019 [cited 2020 Jul 2];(3). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009825.pub3/full

94. Hartley L, Flowers N, Holmes J, Clarke A, Stranges S, Hooper L, et al. Green and black tea for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(6). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009934.pub2/full

95. Cormick G, Ciapponi A, Cafferata ML, Belizán JM. Calcium supplementation for prevention of primary hypertension. Cochrane Database Syst Rev [Internet]. 2015 [cited 2020 Jul 2];(6).

Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010037.pub2/full

96. Flowers N, Hartley L, Todkill D, Stranges S, Rees K. Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(12). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010405.pub2/full

97. Robertson LM, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev [Internet]. 2007 [cited 2020 Jul 2];(4). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002181.pub2/full

98. Hemmingsen B, Gimenez-Perez G, Mauricio D, Figuls MR i, Metzendorf M-I, Richter B. Diet, physical activity or both for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Jul 2];(12). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003054.pub4/full

99. Hartweg J, Perera R, Montori VM, Dinneen SF, Neil AH, Farmer AJ. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Dec 29];(1). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003205.pub2/full

100. Sastre AA, Vernooij RW, Harmand MG-C, Martínez G. Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Dec 29];(6). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003804.pub2/full

101. Norris SL, Zhang X, Avenell A, Gregg E, Brown T, Schmid CH, et al. Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2005 [cited 2020 Jul 2];(2). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004095.pub2/full

102. Nield L, Moore H, Hooper L, Cruickshank K, Vyas A, Whittaker V, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. Cochrane Database Syst Rev [Internet]. 2007 [cited 2020 Jul 2];(3). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004097.pub4/full

103. Duke S-AS, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2009 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005268.pub2/full

104. Dib RE, Gameiro OL, Ogata MS, Módolo NS, Braz LG, Jorge EC, et al. Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance. Cochrane Database Syst Rev [Internet]. 2015 [cited 2020 Jul 2];(5). Available from:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005525.pub3/full

105. Priebe M, Binsbergen J van, Vos R de, Vonk RJ. Whole grain foods for the prevention of type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006061.pub2/full

106. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2009 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006296.pub2/full

107. Jesus CCL de, Atallah ÁN, Valente O, Trevisani VFM. Vitamin C and superoxide dismutase (SOD) for diabetic retinopathy. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006695.pub2/full

108. Leach MJ, Kumar S. Cinnamon for diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007170.pub2/full

109. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007543.pub2/full

110. Pal K, Eastwood SV, Michie S, Farmer AJ, Barnard ML, Peacock R, et al. Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008776.pub2/full

111. Ooi CP, Loke SC. Sweet potato for type 2 diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009128.pub3/full

112. Raval AD, Thakker D, Rangoonwala AN, Gor D, Walia R. Vitamin B and its derivatives for diabetic kidney disease. Cochrane Database Syst Rev [Internet]. 2015 [cited 2020 Jul 2];(1). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009403.pub2/full

113. Thomas D, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. Cochrane Database Syst Rev [Internet]. 2007 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005105.pub2/full

114. Wieland LS, Falzon L, Sciamanna CN, Trudeau KJ, Folse SB, Schwartz JE, et al. Interactive computer-based interventions for weight loss or weight maintenance in overweight or obese people. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Dec 29];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007675.pub2/full

115. Mastellos N, Gunn LH, Felix LM, Car J, Majeed A. Transtheoretical model stages of change for dietary and physical exercise modification in weight loss management for overweight and obese adults. Cochrane Database Syst Rev [Internet]. 2014 [cited 2020 Jul 2];(2). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008066.pub3/full

116. Jurgens TM, Whelan AM, Killian L, Doucette S, Kirk S, Foy E. Green tea for weight loss and weight maintenance in overweight or obese adults. Cochrane Database Syst Rev [Internet]. 2012 [cited 2020 Jul 2];(12). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008650.pub2/full

117. Martin A, Booth JN, Laird Y, Sproule J, Reilly JJ, Saunders DH. Physical activity, diet and other behavioural interventions for improving cognition and school achievement in children and

adolescents with obesity or overweight. Cochrane Database Syst Rev [Internet]. 2018 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009728.pub4/full

118. Tian H, Guo X, Wang X, He Z, Sun R, Ge S, et al. Chromium picolinate supplementation for overweight or obese adults. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(11). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010063.pub2/full

119. Colquitt JL, Loveman E, O'Malley C, Azevedo LB, Mead E, Al-Khudairy L, et al. Diet, physical activity, and behavioural interventions for the treatment of overweight or obesity in preschool children up to the age of 6 years. Cochrane Database Syst Rev [Internet]. 2016 [cited 2020 Dec 29];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012105/full

120. Mead E, Brown T, Rees K, Azevedo LB, Whittaker V, Jones D, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Dec 29];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012651/full

121. Al-Khudairy L, Loveman E, Colquitt JL, Mead E, Johnson RE, Fraser H, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese adolescents aged 12 to 17 years. Cochrane Database Syst Rev [Internet]. 2017 [cited 2020 Dec 29];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012691/full

122. Priest N, Armstrong R, Doyle J, Waters E. Policy interventions implemented through sporting organisations for promoting healthy behaviour change. Cochrane Database Syst Rev [Internet]. 2008 [cited 2020 Jul 2];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004809.pub3/full

123. Hodder RK, O'Brien KM, Tzelepis F, Wyse RJ, Wolfenden L. Interventions for increasing fruit and vegetable consumption in children aged five years and under. Cochrane Database Syst Rev [Internet]. 2020 [cited 2020 Dec 29];(5). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008552.pub7/full

124. Desroches S, Lapointe A, Ratté S, Gravel K, Légaré F, Turcotte S. Interventions to enhance adherence to dietary advice for preventing and managing chronic diseases in adults. Cochrane Database Syst Rev [Internet]. 2013 [cited 2020 Jul 2];(2). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008722.pub2/full

125. Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev [Internet]. 2020 [cited 2020 Dec 29];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011737.pub3/full

126. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med. 2013 Feb 5;158(3):200–7.

127. Schulz KF, Altman DG, Moher D, the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010 Mar 24;8(1):18.

128. Akhter M, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S, et al. Dietary soy and isoflavone intake and risk of colorectal cancer in the Japan public health center-based prospective study. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2008 Aug;17(8):2128–35.

129. Akhter M, Iwasaki M, Yamaji T, Sasazuki S, Tsugane S. Dietary isoflavone and the risk of colorectal adenoma: a case-control study in Japan. Br J Cancer. 2009 Jun 2;100(11):1812–6.

130. Bobe G, Sansbury LB, Albert PS, Cross AJ, Kahle L, Ashby J, et al. Dietary flavonoids and colorectal adenoma recurrence in the Polyp Prevention Trial. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2008 Jun;17(6):1344–53.

131. Cutler GJ, Nettleton JA, Ross JA, Harnack LJ, Jacobs DR, Scrafford CG, et al. Dietary flavonoid intake and risk of cancer in postmenopausal women: the Iowa Women's Health Study. Int J Cancer. 2008 Aug 1;123(3):664–71.

132. Lin J, Zhang SM, Wu K, Willett WC, Fuchs CS, Giovannucci E. Flavonoid intake and colorectal cancer risk in men and women. Am J Epidemiol. 2006 Oct 1;164(7):644–51.

133. Simons CCJM, Hughes LAE, Arts ICW, Goldbohm RA, van den Brandt PA, Weijenberg MP. Dietary flavonol, flavone and catechin intake and risk of colorectal cancer in the Netherlands Cohort Study. Int J Cancer. 2009 Dec 15;125(12):2945–52.

134. Theodoratou E, Kyle J, Cetnarskyj R, Farrington SM, Tenesa A, Barnetson R, et al. Dietary flavonoids and the risk of colorectal cancer. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2007 Apr;16(4):684–93.

135. Wang L, Lee I-M, Zhang SM, Blumberg JB, Buring JE, Sesso HD. Dietary intake of selected flavonols, flavones, and flavonoid-rich foods and risk of cancer in middle-aged and older women. Am J Clin Nutr. 2009 Mar;89(3):905–12.

136. Rosado J. A Study to Determine the Effects of Cinnamon on Blood Glucose and Lipid Levels in Persons with type-2 Diabetes [dissertation]. Honol Univ Hawaii Manoa Honol. 2010;

137. Akilen R, Tsiami A, Devendra D, Robinson N. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabet Med J Br Diabet Assoc. 2010 Oct;27(10):1159–67.

138. Altschuler JA, Casella SJ, MacKenzie TA, Curtis KM. The effect of cinnamon on A1C among adolescents with type 1 diabetes. Diabetes Care. 2007 Apr;30(4):813–6.

139. Blevins SM, Leyva MJ, Brown J, Wright J, Scofield RH, Aston CE. Effect of cinnamon on glucose and lipid levels in non insulin-dependent type 2 diabetes. Diabetes Care. 2007 Sep;30(9):2236–7.

140. Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. J Am Board Fam Med JABFM. 2009 Oct;22(5):507–12.

141. Khan R, Khan Z, Shah SH. Cinnamon May Reduce Glucose, Lipid and Cholesterol Level in Type 2 Diabetic Individuals. Pak J Nutr [Internet]. 2010 [cited 2021 Apr 8]; Available from: https://agris.fao.org/agris-search/search.do?recordID=DJ2012060856

142. Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003 Dec;26(12):3215–8.

143. Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO, et al. Effects of a cinnamon extract on plasma glucose, HbA, and serum lipids in diabetes mellitus type 2. Eur J Clin Invest. 2006 May;36(5):340–4.

144. Suppapitiporn S, Kanpaksi N, Suppapitiporn S. The effect of cinnamon cassia powder in type 2 diabetes mellitus. J Med Assoc Thail Chotmaihet Thangphaet. 2006 Sep;89 Suppl 3:S200-205.

145. Vanschoonbeek K, Thomassen BJW, Senden JM, Wodzig WKWH, van Loon LJC. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. J Nutr. 2006 Apr;136(4):977–80.

146. Woodgate DE, Conquer JA. Effects of a stimulant-free dietary supplement on body weight and fat loss in obese adults: a six-week exploratory study. Curr Ther Res Clin Exp. 2003 Apr;64(4):248–62.

147. Macchi G. A new approach to the treatment of obesity: chitosan's effects on body weight reduction and plasma cholesterol's levels [Un nuovo approccio al trattamento dell'obesita: effetti del chitosano sulla riduzione del peso corporeo e sulla colesterolemia]. Acta Toxicol Ther. 1996;17(4):301–20.

148. Colombo P, Sciutto AM. Nutritional aspects of chitosan employment in hypocaloric diet [Aspetti nutrizionali dell'impiego dell'integratore dietetico chitosano nelle diete ipocaloriche]. Acta Toxicol Ther. 1996;17(4):287–302.

149. Girola M, Bernardi M, Contos S, Tripodi S, Ventura P, Guarino C, et al. Dose effect in lipid-lowering activity of a new dietary integrator (chitosan, Garcinia cambogia extract and chrome) [Effetto della dose sull'attivita antilipemica di un nuovo integratore dietetico (chitosano, estratto di Garcinia cambogia e cromo)]. Acta Toxicol Ther. 1996;17(1):25–40.

150. Giustina A, Ventura P. Weight-reducing regimes in obese subjects: effects of a new dietary fiber integrator [Programmi per la riduzione del peso in pazienti obesi: effetti di un nuovo integratore di fibra dietetica]. Acta Toxicol Ther. 1995;16(4):199–214.

151. Schiller R, Barrager E, Schauss A, Nichols E. A Randomized, Double-Blind, Placebo- Controlled Study Examining the Effects of a Rapidly Soluble Chitosan Dietary Supplement on Weight Loss and Body Composition in Overweight and Mildly Obese Individuals. undefined [Internet]. 2001 [cited 2021 Apr 8]; Available from: /paper/A-Randomized%2C-Double-Blind%2C-Placebo-Controlled-the-Schiller-Barrager/e88244181aa33340fd1c57ed3fa7fe5374a6854f

152. Sciutto AM, Colombo P. Lipid-lowering effect of chitosan dietary integrator and hypocaloric diet in obese subjects [Effetto antilipemico dell'integratore dietetico Chitosano e della dieta ipocalorica in soggetti obesi]. Acta Toxicol Ther. 1995;16(4):215–30.

153. Veneroni G, Veneroni F, Contos S, Tripodi S, De Bernardi M, Guarino C, et al. Effect of a new chitosan dietary integrator and hypocaloric diet on hyperlipidemia and overweight in obese patients [Effetto di un nuovo integratore dietetico a base di chitosano e della dieta ipocalorica sulla dislipidemia ed il sovrappeso in pazienti obesi]. Acta Toxicol Ther. 1996;17(1):53–70.

154. Wuolijoki E, Hirvelä T, Ylitalo P. Decrease in serum LDL cholesterol with microcrystalline chitosan. Methods Find Exp Clin Pharmacol. 1999 Jun;21(5):357–61.

155. Pittler MH, Abbot NC, Harkness EF, Ernst E. Randomized, double-blind trial of chitosan for body weight reduction. Eur J Clin Nutr. 1999 May;53(5):379–81.

156. Ho SC, Tai ES, Eng PH, Tan CE, Fok AC. In the absence of dietary surveillance, chitosan does not reduce plasma lipids or obesity in hypercholesterolaemic obese Asian subjects. Singapore Med J. 2001 Jan;42(1):6–10.

157. Kaats GR, Michalek JE, Preuss HG. Evaluating efficacy of a chitosan product using a double-blinded, placebo-controlled protocol. J Am Coll Nutr. 2006 Oct;25(5):389–94.

158. Mhurchu CN, Poppitt SD, McGill A-T, Leahy FE, Bennett DA, Lin RB, et al. The effect of the dietary supplement, Chitosan, on body weight: a randomised controlled trial in 250 overweight and obese adults. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2004 Sep;28(9):1149–56.

159. Williams AR. A double-blind, placebo-controlled evaluation of the effects of RW94 on the body weight of both overweight and obese healthy volunteers. Curr Med Res Opin. 1998;14(4):243–9.

160. Mabuchi H, Nohara A, Kobayashi J, Kawashiri M, Katsuda S, Inazu A, et al. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007 Dec;195(2):e182-189.

161. Yamagami T, Takagi M, Akagami H, Kubo H, Toyama S, Okamoto T. Elect of coenzyme Q10 on essential hypertension, a double blind controlled study. Biomedical and Clinical Aspects of Coenzyme Q10: Proceedings of the FiPh International Symposium on the Biomedical and Clinical Aspects of Coenzyme Q1. Proc FiPh Int Symp Biomed Clin Asp Coenzyme Q10. 1986;5:337–43.

162. Adarsh K, Kaur H, Mohan V. Coenzyme Q10 (CoQ10) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). BioFactors Oxf Engl. 2008;32(1–4):145–9.

163. Berman M, Erman A, Ben-Gal T, Dvir D, Georghiou GP, Stamler A, et al. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. Clin Cardiol. 2004 May;27(5):295–9.

164. Keogh A, Fenton S, Leslie C, Aboyoun C, Macdonald P, Zhao YC, et al. Randomised double-blind, placebo-controlled trial of coenzyme Q, therapy in class II and III systolic heart failure. Heart Lung Circ. 2003;12(3):135–41.

165. Khatta M, Alexander BS, Krichten CM, Fisher ML, Freudenberger R, Robinson SW, et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med. 2000 Apr 18;132(8):636–40.

166. Kocharian A, Shabanian R, Rafiei-Khorgami M, Kiani A, Heidari-Bateni G. Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy. Cardiol Young. 2009 Sep;19(5):501–6.

167. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. Clin Investig. 1993;71(8 Suppl):S134-136.

168. Munkholm H, Hansen HH, Rasmussen K. Coenzyme Q10 treatment in serious heart failure. BioFactors Oxf Engl. 1999;9(2–4):285–9.

169. Bargossi AM, Grossi G, Fiorella PL, Gaddi A, Di Giulio R, Battino M. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. Mol Aspects Med. 1994;15 Suppl:s187-193.

170. Kaikkonen J, Nyyssönen K, Tomasi A, Iannone A, Tuomainen TP, Porkkala-Sarataho E, et al. Antioxidative efficacy of parallel and combined supplementation with coenzyme Q10 and d-alpha-tocopherol in mildly hypercholesterolemic subjects: a randomized placebo-controlled clinical study. Free Radic Res. 2000 Sep;33(3):329–40.

171. Lee Y-J, Cho W-J, Kim J-K, Lee D-C. Effects of coenzyme Q10 on arterial stiffness, metabolic parameters, and fatigue in obese subjects: a double-blind randomized controlled study. J Med Food. 2011 Apr;14(4):386–90.

172. Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, George PM, et al. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007 Nov 1;100(9):1400–3.

173. Ferraro S, Codella C, Palumbo F, Desiderio A, Trimigliozzi P, Maddalena G, et al. Hemodynamic effects of creatine phosphate in patients with congestive heart failure: a double-blind comparison trial versus placebo. Clin Cardiol. 1996 Sep;19(9):699–703.

174. Gordon A, Hultman E, Kaijser L, Kristjansson S, Rolf CJ, Nyquist O, et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. Cardiovasc Res. 1995 Sep;30(3):413–8.

175. Grazioli I, Melzi G, Strumia E. Multicenter controlled study of creatine phosphate in the treatment of heart failure. Curr Ther Res. 1992 Aug 1;52(2):271–80.

176. Kuethe F, Krack A, Richartz BM, Figulla HR. Creatine supplementation improves muscle strength in patients with congestive heart failure. Pharm. 2006 Mar;61(3):218–22.

177. Ruda MYa null, Samarenko MB, Afonskaya NI, Saks VA. Reduction of ventricular arrhythmias by phosphocreatine (Neoton) in patients with acute myocardial infarction. Am Heart J. 1988 Aug;116(2 Pt 1):393–7.

178. Auer W, Eiber A, Hertkorn E, Hoehfeld E, Koehrle U, Lorenz A, et al. Hypertension and hyperlipidaemia: garlic helps in mild cases. Br J Clin Pract Suppl. 1990 Aug;69:3–6.

179. Kuethe F, Krack A, Richartz BM, Figulla HR. Creatine supplementation improves muscle strength in patients with congestive heart failure. Pharm. 2006 Mar;61(3):218–22.

180. Schiller RN, Barrager E, Schauss AG, Nichols EJ. A randomized, double-blind, placebo-controlled study examining the effects of a rapidly soluble chitosan dietary supplement on weight loss and body composition in overweight and mildly obese individuals. J Am Nutraceutical Assoc. 2001;4:42–9.

181. Mbuagbaw L, Kredo T, Welch V, Mursleen S, Ross S, Zani B, et al. Critical EPICOT items were absent in Cochrane human immunodeficiency virus systematic reviews: a bibliometric analysis. J Clin Epidemiol. 2016 Jun;74:66–72.

182. Chartres N, Fabbri A, McDonald S, Diong J, McKenzie JE, Bero L. Association of food industry ties with findings of studies examining the effect of dairy food intake on cardiovascular disease and mortality: systematic review and meta-analysis. BMJ Open. 2020 Dec 1;10(12):e039036.

183. Chartres N, Fabbri A, McDonald S, Turton J, Allman-Farinelli M, McKenzie J, et al. Association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: systematic review and meta-analysis. BMJ Open. 2019 May 1;9(5):e022912.

184. Fabbri A, Chartres N, Scrinis G, Bero LA. Study sponsorship and the nutrition research agenda: analysis of randomized controlled trials included in systematic reviews of nutrition interventions to address obesity. Public Health Nutr. 2017 May;20(7):1306–13.

185. Fabbri A, Chartres N, Bero LA. Study sponsorship and the nutrition research agenda: analysis of cohort studies examining the association between nutrition and obesity. Public Health Nutr. 2017 Dec;20(17):3193–9.

186. Benea C, Turner KA, Roseman M, Bero LA, Lexchin J, Turner EH, et al. Reporting of financial conflicts of interest in meta-analyses of drug trials published in high-impact medical journals: comparison of results from 2017 to 2018 and 2009. Syst Rev. 2020 Apr 8;9(1):77.

187. Chartres N, Fabbri A, Bero LA. Association of Industry Sponsorship With Outcomes of Nutrition Studies: A Systematic Review and Meta-analysis. JAMA Intern Med. 2016 Dec 1;176(12):1769–77.

188. McCarthy M. PubMed is urged to include competing interest information in abstracts. BMJ. 2016 Apr 7;353:i2018.

189. Pedone V. An assessment of the activity of creatine phosphate (Neoton) on premature ventricular beats by continuous ECG monitoring in patients with coronary cardiac disease. Clin Trials J. 1984;21(2):91–9.

190. Pedone V, C C, Frondini C, Franchi R, Luppi, Luppi M, et al. Myocardial T1-201 scintigraphy in the study of the development of acute myocardial infarction. Evaluation of the effects of a drug with metabolic action: creatine phosphate [la scintigrafia miocardica con T1–201 nello studio dell'evolutione dell'infarto miocardico acuto (AMI): Valutazione degli effetti di un farmaco ad azione metabolica: la creatina fosfato]. Clin Ter. 1984;111(6):531–8.

191. Samarenko MB, Afonskaia NI, Dvoskina IS, Ruda MI. [Initial experience with using phosphocreatine in patients in the early (up to 6 hours) period of myocardial infarction]. Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR. 1987;10(2):75–81.

192. Zahorska-Markiewicz B, Krotkiewski M, Olszanecka-Glinianowicz M, Zurakowski A. Effect of chitosan in complex management of obesity [Ocena Zastosowania chitosanu w kompleksowym leczeniu otylosci]. Pol Merkuriusz Lek. 2002;13(74):129–32.

193. Carmenini G. Controlled multicentric clinical study with placebo in patients with dilatative myocardiopathy functional class II-III N.Y.H.A. treated with oral phosphocreatinine. CUORE Riv CARDIOCHIRURGIA E Cardiol. 1994;11(2):187–93.

194. Maggi GC, Lomanto B, Mazzola C. Double-blind multicenter clinical trial on the efficacy of phosphocreatinine vs L-carnitine and placebo in a group of patients affected by heart disease

[Studio clinico in doppio cieco multicentrico sull'efficacia di fosfocreatinina vs L–carnitina e placebo in un gruppo di cardiopatici]. Acta Toxicol Ther. 1990;11(2):173–84.

195. Zochowski RJ, Sobieszczańska-Małek M, Komuda K. [Use of phosphocreatinine in treatment of acute heart failure]. Pol Tyg Lek Wars Pol 1960. 1994 Jun 20;49(25–26):576–8.

196. Kandaziora_J. Blood pressure and lipid lowering effect of garlic preparations in combination with a diuretic [Blutdrukund lipidsenkende Wirkung eines Knoblauch-Praparates in Kombination mit einem Diuretikum]. Artzliche Forsch. 1988;35:1–8.

197. Terzic A, Waldman S. Chronic Diseases: The Emerging Pandemic. Clin Transl Sci. 2011 Jun 1;4(3):225–6.

198. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2016 Aug 14]. Available from: http://handbook.cochrane.org/

199. 12 Interpreting results and drawing conclusions [Internet]. [cited 2016 Jul 22]. Available from: http://handbook.cochrane.org/chapter_12/12_interpreting_results_and_drawing_conclusions.htm

200. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15;7:10.

201. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013–20.

202. Seo H-J, Kim KU. Quality assessment of systematic reviews or meta-analyses of nursing interventions conducted by Korean reviewers. BMC Med Res Methodol. 2012 Aug 28;12:129.

203. Petryna A. Ethical variability: Drug development and globalizing clinical trials. Am Ethnol. 2005 May 1;32(2):183–97.

Additional Files

Table a1: Characteristics of Cochrane nutrition reviews addressing cancer

Domain	Characteristics
NCD Grouping or nutrition- related risk factors	Cancer
Number of reviews(n/N) %	15/98 (15.3%)
NCDs and nutrition related risk factors addressed in review	Cancer, Gastrointestinal cancer, neuroblastoma, head and neck cancer, colorectal cancer, colorectal carcinoma, colorectal neoplasms, cancer cachexia, prostate cancer and adenomatous polyps
Population	**Healthy people** :adults ≥ 18 years **People at high risk** e.g. high risk of gastrointestinal cancer, People with high-risk neuroblastoma, Healthy adults at higher risk of colon cancer due to family history, previous adenomatous polyps, or inflammatory bowel disease. **People with disease**: e.g. people with non-gastrointestinal cancer, cancer patients (adults and children ages > 1 year) who received chemotherapy causing neutropenia, adult patients with head and neck cancer receiving radiotherapy and/or chemotherapy, Children and young people (ages≤ 21 years) with malignant disease, patients with incurable or advanced cancer and cachexia **People with comorbidities** e.g. Adult participants (aged 18 years or over) with vitamin D deficiency or a disease but are in stable condition
Intervention	**Foods** e.g. green tea, **Diets and dietary patterns** e.g. low bacterial diets, **Feeding modalities** e.g. enteral feeding for head and neck cancer **Nutritional products and nutrients and bioactive non-nutrients** e.g. antioxidants (selenium, Vitamin C, Vitamin D), dietary fiber **Nutrition education and counselling programmes** e.g. nutritional support
Years Reviews published	2007 to 2020

Table a2: Characteristics of Cochrane nutrition reviews addressing cardiovascular diseases

Domain	Characteristics
NCD Grouping of nutrition related risk factors	Cardiovascular diseases
Number of reviews(n/N)%	40/98 (40.8%)
NCDs and nutrition related risk factors addressed	Cardiovascular diseases, myocardial infaction, heart failure, coronary heart disease, stroke, blood pressure/hypertension, peripheral arterial occlusive disease (PAOD), arterial or venous leg ulcers, intermittent claudation, peripheral arterial disease of the lower limb, cholesteroleamia
Population	**Healthy people** :adults ≥ 18 years without cardiovascular disease, normotensive people of different ages **People at high risk** e.g. Adults ages≥18 with essential hypertension at any risk, Persons with normal or elevated blood pressure, Adults of all ages at high risk of cardiovascular diseases, Participants with history of stroke **People with disease**: e.g. Adults ages≥18 years with existing cardiovascular disease (myocardial infarction, chronic heart failure, peripheral arterial occlusive disease, intermittent claudication, lower limb peripheral arterial disease (PAD)) **People with comorbidities** e.g. Adults ages≥18 with essential hypertension at any risk, diagnosed as overweight or obese, children and adults with familial hypercholesterolaemia, acquired (not familial) hypercholesterolaemia
Intervention	**Foods** e.g. cocoa powder, garlic, green or black tea, **Nutritional products and nutrients and bioactive non-nutrients**: oral zinc sulphate, potassium, calcium, selenium, Coenzyme Q10. **Diets and dietary patterns** e.g. Mediterranean-style diet, lipid lowering diet, increased vegetable consumption **Nutrition education and counselling programmes** e.g. dietary advice to reduce blood cholesterol, dietary interventions involve verbal or written advice
Year reviews published	1998 to 2000

Table a3: Characteristics of Cochrane reviews addressing chronic respiratory diseases

Domain	Characteristics
NCD Grouping of nutrition related risk factors	Chronic Respiratory diseases
Number of reviews(n/N)%	15/98 (15.3%)
NCDs and nutrition related risk factors addressed	Asthma
Population	**People at high risk** e.g. Children at high risk of developing atopy or asthma **People with disease**: e.g. Adults and children with allergic asthma (e.g. sensitivity to aspirin or tartrazine), exercise induced asthma and bronchoristiction and overweight or obese adults and children with asthma
Intervention	**Foods** e.g. Caffeine or coffee, **Nutritional products and nutrients and bioactive non-nutrients**: selenium, tartrazine, Vitamin C, Vitamin E, **Diets and dietary patterns** e.g. dietary calorie reduction, marine n-3 fatty acids to the diet and/or any manipulation of dietary intake of marine n-3 fatty acids, allergen reducing interventions (inhalant allergens and/or food allergens)
Years Reviews published	2004 to 2014

Table a4: Characteristics of Cochrane nutrition reviews addressing diabetes

Domain	Characteristics
NCD Grouping of nutrition related risk factors	Diabetes
Number of reviews(n/N)%	17/98 (17.3%)
NCDs and nutrition related risk factors addressed	Cognitive impairment and dementia, Type 1 and 2 Diabetes, Diabetes Kidney disease, Diabetic neuropathy
Population	**People at high risk** e.g. Healthy individuals with/ at least one major risk factor for type 2 diabetes, prediabetic individuals, Individuals with insulin resistance **People with disease**: e.g. Adults with diabetic retinopathy, diabetic retinopathy, diabetes kidney disease, individuals with type 1 or type 2 diabetes.
Intervention	**Foods** e.g whole grain foods, , **Nutritional products and nutrients and bioactive non-nutrients**: vitamin C/superoxidase dismutase, Vitamin B, cinnamon,zinc **Diets and dietary patterns** e.g Diet with or without physical activity, , low glycaemic index (GI) or low glycaemic load diet **Nutrition education and counselling programmes** e.g individual patient education for managing type 2 diabetes, dietary advice for reducing weight and severity of type 2 diabetes, Computer-based software applications for self-management of type 2 diabetes **Policy programmes or system programmes** e.g treatment approved by international guidelines for Type 2 diabetes
Years Reviews published	2005 to 2017

Table a5: Characteristics of Cochrane nutrition reviews addressing obesity and overweight

Domain	Characteristics
NCD Grouping or nutrition related risk factors	Obesity and overweight
Number of reviews(n/N)%	12/98 (12.2%)
Non-communicable Diseases or nutrition related risk factors	Overweight and obesity
Population	**People with disease**: e.g overweight or obese individuals (children and adolescents ages 0 to 18 years and adults ages≥ 18 years) , fully-qualified health professionals, working with adults and children with overweight or obesity, in healthcare settings
Intervention	**Foods** e.g green tea **Nutritional products and nutrients and bioactive non-nutrients**: Chromium picolinate (CrP),chitosan, **Diets and dietary patterns** e.g. dietary, physical activity and/or behavioural therapy for weight loss, Physical, psychological and Dietary and nutritional interventions, low glycaemic index or low glycaemic load diet **Nutrition education and counselling programmes** e.g. intervention directed at the healthcare professional or organisation of care to help implement weight reduction interventions in children and adults with overweight or obesity. Transtheoretical model (TTM) stages of change (SOC) combined with dietary and /or physical activity intervention. Computer-based weight loss or weight maintenance program
Years Reviews published	2007-2019

Table a6: Characteristics of Cochrane nutrition reviews addressing healthy diets

Domain	Characteristics
NCD Grouping or nutrition related risk factors	Healthy diets
Number of reviews(n/N)%	3/98 (3.1%)
Non-communicable Diseases or nutrition related risk factors	Chronic Diseases, healthy diets, healthy behavior change
Population	**Healthy individuals** e.g. children ages≤ five years ,Individuals ages ≤18 years,People of all ages
Intervention	**Nutrition education and counselling programmes** e.g. educational, experiential, health promotion and/or psychological or family or behavioural therapy or counselling or management or structural or policy or legislative reform interventions, designed to increase consumption of fruit or vegetables or both, chronic disease prevention and management for adherence to dietary advice. **Policy programmes or system programmes** e.g policy intervention implemented through sporting organisations to instigate and/ or sustain healthy behaviour change, intention to change behaviour, or changes in attitudes, knowledge or awareness of healthy behaviour
Years Reviews published	2008-2020

Table a7: Characteristics of included primary studies included in Cochrane nutrition reviews addressing the four major NCDs and their nutrition related risk factors

Table a7 is a table of characteristics of the full-text English primary studies (n=51) included in Cochrane nutrition reviews addressing alternative nutrition supplements and the four major NCDs and their nutrition related risk factors.

Cochrane review title (Accession number)	**Chitosan for overweight or obesity (CD003892) (34)**
Colombo 1996	
Study Title	Nutritional aspects of chitosan employment in hypocaloric diet (148)
Non communicable disease	NA
Nutrition-related risk factor	Overweight and obesity
Population	Ambulatory males and females aged 20-70 years with mild obesity (overweight by 10% to 25% as compared with ideal weight-height tables) and hyper lipoproteinemia.
Intervention	2 capsules twice daily (dose not stated) of "Somagril" (Lifepharma) (chitosan, guar's meal, ascorbic acid and other micronutrients) with meals (lunch/dinner). Co-interventions :Low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Comparison	2 capsules twice daily (dose and composition not stated).capsules advised to be taken with main meals (lunch/dinner). Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Outcome	Outcomes assessed following 4 weeks of treatment: Body weight, percentage overweight, serum lipids, side effects, quality of life, diet and drug compliance, appearance of faeces, haematological and blood chemistry analysis
Study Design	Parallel randomised Control Trial
Country	Italy
Conflict of interest disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA

Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Girola 1996	
Study Title	Dose effect in lipid-lowering activity of a new dietary integrator (chitosan, Garcinia cambogia extract and chrome)(149)
Non-communicable disease	NA
Nutrition-related risk factor	Overweight and obesity
Population	Ambulatory males and females aged 20-70 years with mild obesity (overweight by 10% to 25% as compared with ideal weight-height tables) and hyper lipoproteinemia.
Intervention	Group 1: 2 capsules daily of "Colenon" (480 mg chitosan, garcinia cambogia extract and chrome) during main meals (lunch/dinner). Group 2: 1 capsule daily of "Colenon" (240mg chitosan, garcinia cambogia extract and chrome) during main meals (lunch/dinner). Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Comparison	2 capsules daily (composition not stated) during with main meals (lunch/dinner). Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Outcome	Outcomes assessed following 4 weeks of treatment: Body weight, percentage overweight, serum lipids, side effects, quality of life, diet and drug compliance, appearance of faeces, haematological and blood chemistry analysis.
Study Design	Parallel randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA

Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA
Giustina 1995	
Study Title	Weight-reducing regimes in obese subjects: effects of anew dietary fiber integrator (150)
Non-communicable disease	NA
Nutrition-related risk factor	Overweight and obesity
Population	Ambulatory males and females aged 20-70 years with mild obesity (overweight by 10% to 25% as compared with ideal weight-height tables) and mild hypertension.
Intervention	2 tablets twice daily of "Nofat" (chitosan, guar's meals, ascorbic acid and other micronutrients) during main meals (lunch/dinner). Co-interventions: low calorie diet(1000-100kcal based on 34% fat, 41% carbohydrate and 25% protein)
Comparison	2 tablets twice daily (composition not stated) during main meals (lunch/dinner). Co-interventions: low calorie diet(1000-100kcal based on 34% fat, 41% carbohydrate and 25% protein)
Outcome	Body weight, percentage overweight, arterial pressure (systolic and diastolic), heart, respiratory rate, side effects, quality of life, diet and drug compliance and appearance of faeces were assessed at 7,14, 21, and 28 days of treatment. Hematological and blood chemistry analysis at 28 days post treatment
Study Design	Parallel randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No

Name of Author-financial sponsor ties	NA
Author's conclusions	NA
Ho 2001	
Study Title	In the absence of dietary surveillance, chitosan does not reduce plasma lipids or obesity in hypercholesterolaemic obese asian subject (156)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Normoglycaemic obese males and females (body fat % > 20% in males and > 30% in females) who were hypercholesterolaemic (total cholesterol>5.20 mmol/L) and had no history of chronic illnesses.
Intervention	Run-in phase comprising the first 4 weeks followed by 4 capsules of 257 mg "Absorbitol" (257 mg ShellfishL112 Absorbitol, 175 mg corn starch, 10 mg calcium carbonate, 5 mg magnesium stearate) 3 times daily for 12 weeks. Co-interventions: no dietary restriction
Comparison	Run-in phase comprising the first 4 weeks followed by 4 capsules of placebo (450 mg cornstarch) 3 times daily for 12 weeks, Co-interventions: no dietary restriction
Outcome	Outcomes assessed at enrolment, baseline (following 4 weeks placebo run-in phase) and after 12 weeks of treatment: Body weight, BMI, waist and hip circumferences, blood pressure (systolic and diastolic), fat free mass, % body fat, serum lipids, and fasting insulin, adverse events.
Study Design	Parallel randomised Control Trial
Country	Singapore
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Kaats 2006	
Study Title	Evaluating efficacy of a chitosan product using a double-blinded, placebo controlled protocol (157)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Overweight Adults.
Intervention	6 tablets of 500 mg chitosan, and 1mg per tablet of beta-glucan, snow white oat fibre, betamine HCL and aloe saponins daily .Co-interventions: Self-monitored behavioural modification programme consisting of a work book for estimating caloric intake, calculator with nutritional information on 5000 foods, log book for calculating and estimating daily calorie balances and dietary fat intake, pedometer and recording of daily steps
Comparison	Placebo group: 6 tablets of Polylactic acid daily.Co-interventions: Self-monitored behavioral modification programme consisting of a work book for estimating caloric intake, calculator with nutritional information on 5000 foods, log book for calculating and estimating daily calorie balances and dietary fat intake, pedometer and recording of daily steps Control group: Minimum intervention group which followed a programme of their own choosing
Outcome	Outcomes assessed at baseline and after 60 days of treatment: Body weight (lbs), fat mass, fat free mass, % body fat, serum lipids
Study Design	Parallel randomised Control Trial
Country	United States of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Health and Medical Research Center , San Antonio Texas
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Macchi 1996	
Study Title	A new approach to the treatment of obesity: chitosan's effects on body weight reduction and plasma cholesterol's levels(147)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and Overweight
Population	Obese males and females aged 30 and 80 years old, with 25% excess body weight.
Intervention	4 tablets 250 mg of chitosan (purified electrostatically charged chitosan (PAT RM q5A 000 772).) daily ,just before main meals. Co-interventions: low calorie diet (1200 kcal based on 30% fat, 45% carbohydrate and 25% protein)
Comparison	Comparator 1: 4 placebo tablets daily (composition not stated) just before main meals Co-interventions: low calorie diet (1200 kcal based on 30% fat, 45% carbohydrate and 25% protein); Comparator 2: 4 placebo tablets daily (composition not stated). Capsules advised to be taken just before main meals. Co-interventions: none (usual diet)
Outcome	Body weight, BMI, % body fat, emochrome, iron, electrolytes, transaminase, lipids, glucose, urea nitrogen and creatinine, side effects, well-being and appetite.
Study Design	Parallel randomised control trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA
Ni Mhurchu 2004	

Study Title	The effect of the dietary supplement, chitosan, on body weight: a randomised controlled trial in 250 overweight and obese adults(158)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Overweight or obese (BMI 28-50kg/m2) males and females ages≥ 18 years who wished to lose weight.
Intervention	4 capsules of 250 mg chitosan (beta-chitosan derived from NZ squid pens, molecular weight of 130,000, and deacetylation was 75.5%.) three times daily for 24 weeks, 30 minutes before meals. Co-interventions: standardised dietary and lifestyle advice
Comparison	4 capsules of 250 mg maize cornflour three times daily for 24 weeks. Co-interventions: standardised dietary and lifestyle advice
Outcome	Outcomes assessed at 4-weekly visits and overall response was measured over entire 24-week period: Body weight, BMI, waist circumference, % fat, blood pressure (systolic and diastolic), glucose, serum lipids, vitamin A, beta-carotene, vitamin D, prothrombin time, health-related quality of life, adverse events, adherence to treatment, faecal fat (subgroup of 50 volunteers) .
Study Design	Parallel randomised Control Trial
Country	New Zealand
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Health research Council of New Zealand and Healtheries of New Zealand Ltd
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	CNM and AR held fellowships from the National Heart Foundation of New Zealand
Author's conclusions	Unfavourable to financial sponsor and author-financial sponsor ties

Pittler 1999	
Study Title	Randomized, double-blind trial of chitosan for body weight reduction(155)
Non-communicable disease	NA

Nutrition-related risk factor	Obesity and overweight
Population	Participants 18 to 60 years of age, BMI ranging from 23.9±28.5kg/m2 for women and 25.0±29.9kg/m2 for men.
Intervention	4 capsules of 250mg chitosan (deacetylated chitin biopolymer) daily for 28 consecutive days. Co-interventions: normal diet
Comparison	4 capsules of indistinguishable placebo twice daily for 28 consecutive days. Co-interventions: normal diet.
Outcome	Medical history taken at baseline. Dietary intake recorded in food diary, routine glucose measurement, body weight, height, blood pressure and quality of life using the SF-36, Blood concentration of total cholesterol, triglycerides, vitamin A, D (as 25-hydroxy vitamins D2 and D3), E, and K, and b-carotene, frequency of adverse effects (AEs) all at baseline, after 14 and 28 days of treatment. Compliance was monitored by counting the remaining capsules after the final study visit.
Study Design	Parallel randomised Control Trial
Country	United Kingdom
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Marshtech Ltd, London
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsor and author-financial sponsor ties

Schiller 2001	
Study Title	A randomized, double-blind, placebo-controlled study examining the effects of a rapidly soluble chitosan dietary supplement on weight loss and body composition in overweight and mildly obese individuals(180)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Overweight and mildly obese (BMI 27-40) but otherwise healthy females aged 21-55 years, with a stable weight history of at least 6

	months and a history of daily fat consumption greater than or equal to 30% of calories.
Intervention	3 capsules of 500 mg LipoSan Ultra (>90% chitosan and <10% succinicacid, deacetylation value of >78%, viscosity of approx. 155 mPas, molecular weight >100,000 daltons) twice daily for 8 weeks e taken immediately prior to 2 largest meals of the day. Co-interventions: normal diet or exercise routines
Comparison	3 capsules of 500 mg maltodextrin-semolina flour blend twice daily for 8 weeks. Co-interventions: normal diet or exercise routines
Outcome	Outcomes assessed at baseline and 8 weeks: Body weight, BMI, waist-to-hip ratio, % body fat, % lean body mass, fasting serum lipid levels, fecal fat (in a subset of 7 participants). Beck depression inventory, medical outcome survey (short form 36), diet (food frequency questionnaire and diet diary), functional gastrointestinal and elimination symptoms.
Study Design	Parallel randomised Control Trial
Country	United States of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Vanson Inc
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor
Sciutto 1995	
Study Title	Lipid-lowering effect of chitosan dietary integrator and hypocaloric diet in obese subjects(152)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Ambulatory males and females aged 20-70 years with mild obesity (overweight by 10% to 25% as compared with ideal weight-height tables), mild hypertension, and hyper lipoproteinemia.

Intervention	2 tablets twice daily of "Somagril" (chitosan, guar's meals, ascorbic acid and other micronutrients) for 4 weeks taken with main meals lunch/dinner). Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Comparison	2 placebo tablets 500mg of the maltodextrin-semolina flour blend twice daily for 4 weeks. Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Outcome	Body weight, percentage overweight, arterial pressure (systolic and diastolic), incidence of side effects, quality of life, diet and drug compliance, appearance of faeces were assessed at 7, 14, 21, and 28 days of treatment. Serum cholesterol triglycerides, were assessed at 0, 7, and 28 days. Hematological and blood chemistry analysis (were assessed at 0 and 28 days
Study Design	Parallel randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Veneroni 1996	
Study Title	Effect of a new chitosan dietary integrator and hypocaloric diet on hyperlipidemia and overweight in obese patients(153)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Ambulatory males and females aged 20-70 years with mild obesity (overweight by 10% to 25% as compared with ideal weight-height tables), and hyperlipidemia.

Intervention	2 tablets of "Nofat" (chitosan, guar's meals, ascorbic acid and other micronutrients) for 4 weeks twice daily taken with main meals (lunch/dinner).Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Comparison	2 tablets twice daily for 4 weeks with main meals (lunch/dinner. Co-interventions: low calorie diet (1000 kcal based on 34% fat, 41% carbohydrate and 25% protein)
Outcome	Body weight, percentage overweight, diet, physical fitness program and drug compliance, appearance of faeces, incidence of adverse events, quality of life were assessed at 0, 7, 14, 21, and 28 days of treatment. Serum cholesterol, triglycerides, hematological and blood chemistry analysis were assessed at 0 and 28 days of treatment.
Study Design	Parallel randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Williams 1998	
Study Title	A double-blind, placebo-controlled evaluation of the effects of RW94 on the body weight of both overweight and obese healthy volunteers(159)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Male and female adult volunteers aged 23-57 years, healthy but otherwise overweight meeting standard inclusion criteria for Phase I clinical trials.

Intervention	5g RW94 powder stirred into a glass of fruit squash 3 times daily for 6 weeks taken 30 minutes after food. Co-interventions: normal diet, smoking or drinking habits
Comparison	5g maize starch stirred into a glass of fruit squash 3 times daily for 6 weeks taken 30 minutes after food. Co-interventions: normal diet, smoking or drinking habits
Outcome	Outcomes assessed at 0, 1, 2, 3, 4, 5, and 6 weeks: Body weight, state of health, adverse events.
Study Design	Parallel randomised Control Trial
Country	United Kingdom
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Woodgate 2003	
Study Title	Double-blind study evaluating the effects of a proprietary blend of glucomannan and chitosan on weight loss in overweight adults/ Effects of a stimulant-free dietary supplement on body weight and fat loss in obese adults: a six-week(146)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Obese (BMI >/= 30) male and female volunteers aged 20- 50 years.
Intervention	2 capsules of chitosan (glucomannan, chitosan, fenugreek, G sylvestre, and vitamin C (1 capsule = 1395 mg) three times daily for 6 weeks taken before 1 hour meals.Co-interventions: participants instructed to continue their regular diet and exercise patterns
Comparison	2 capsules of rice flour three times daily for 6 weeks taken before 1 hour meals.Co-interventions: normal diet and exercise patterns

Outcome	Measured at baseline and 6 weeks: Body weight, % body fat, fat mass, lean body mass, BMI, blood pressure, resting heart rate, upper abdominal circumference, waist and hip circumferences.
Study Design	Parallel randomised Control Trial
Country	Canada
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	NxCare Inc. (Guelph, Ontario, Canada)
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	Derek E. Woodgate, MSc, stated that He is the president and owner of NxCare Inc.,which produces the dietary supplement containing glucomannan, chitosan, fenugreek, Gymnema sylvestre, and vitamin C (trade name Calorie-Care) which were used in the study.
Author's conclusions	Favourable to financial sponsor and author-financial sponsor ties

Wuolijoki 1999	
Study Title	Decrease in Serum LDL Cholesterol with Microcrystalline Chitosan(154)
Non-communicable disease	NA
Nutrition-related risk factor	Obesity and overweight
Population	Healthy women ages 18 to 60 years, BMI of 28-34.99, using a reliable contraceptive (in women at fertile age).
Intervention	3 capsules containing microcrystallined chitosan (400 mg + 50 mg auxiliary agents/capsule daily taken just before lunch and dinner for 8 weeks.Co-interventions: normal living routines and diet
Comparison	3 capsules of starch 2 times daily taken just before lunch and dinner for 8 weeks. Co-interventions: normal living routines and diet.
Outcome	Serum Lipids Fe++, transferrin, total A and E vitamins, alanine-amino transferase (ALAT), aspartate-amino transferase (ASAT), alkaline phosphatase, creatinine, Na+, K+, adverse events, body weight, and compliance
Study Design	Parallel Randomised control trial
Country	Finland
COI disclosed	No

Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Cochrane Review title (Accession number): Creatine and creatine analogues in hypertension and cardiovascular disease (CD005184) (83)	
Ferraro 1996	
Study Title	Hemodynamic effects of creatine phosphate in patients with congestive heart failure: a double-blind comparison trial versus placebo(173)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Hospitalised patients (12 men, 1 woman, mean age 52 ± 8 years) with Heart failure. NYHA class II-II
Intervention	Intravenous infusion of 6 gram creatine phosphate followed by 2 days' washout interval from CP, followed by a 4-day treatment period of placebo(50 mg mannitol) daily in two intravenous administrations, diluted in 50ml NaCl 0.9%
Comparison	Intravenous infusion of placebo(50 mg mannitol), followed by 2 days' washout interval from placebo followed by a 4-day treatment period of receiving 6 gram creatine phosphate daily in two intravenous administrations, diluted in 50ml NaCl 0.9%
Outcome	Mono-bidimensional echo at baseline,15 rnh after treatment infusion, and 12 h after the end of short-term CP or placebo infusion on the basis of the pharmacokinetics and pharmacodynamics of **CP.'O,** ' systolic and diastolic blood pressure and heart rate(HR); mean blood pressure(MAP) , echo parameters: end-diastolic diameter (EDD), end-systolic diameter (ESD), percent fractional shortening **(%FS)**, end-diastolic volume (EDV) and end-systolic volume (ESV),Percent ejection fraction (%EF),systemi vascular resistance **(SVR)**
Study Design	double-blind, crossover, placebo-controlled

Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Gordon 1995	
Study Title	Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance.(174)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Male patients with heart failure (HF) aged 43-70 years, ejection fraction (EF) < without intermittent claudication, diabetes mellitus, chronic obstructive pulmonary disease, neurologic disease or any other disease which may limit physical performance other than heart failure ,exertional Angina, significant valvular heart disease as estimated by Doppler echocardiography. All patients were medicated with diuretics, angiotensin-converting enzyme inhibitors, digoxin, beta-receptor blockers, amiodarone and on warfarin
Intervention	creatine supplementation(with glucose) for 1 week
Comparison	placebo (glucose) for 1 week
Outcome	Knee extensor exercise, Two-legged cycle ergometry (heart rate and blood Pressure and working capacity) were measured, Unilateral concentric knee extensor performance and Skeletal muscle biopsies. Metabolites: muscle total creatine and phosphocreatine and creatine. Radionuclide angiography at rest and during exercise
Study Design	Parallel randomised Control Trial
Country	Sweden
COI disclosed	No
Financial sponsor disclosed	Yes

Name of Financial sponsor	Swedish Medical Research Council (4494 and 9515), the Swedish Heart and Lung Foundation and the Salus 60-year Medical Foundation.
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Grazioli 1992	
Study Title	Multicenter controlled study of creatine phosphate in the treatment of heart failure.(175)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	patients hospitalised for heart failure;
Intervention	One gram CrP intravenously daily added to conventional treatment or no added treatment for two weeks (acute treatment) followed by 500 mg CrP intramascularly daily or no added treatment for 1 month
Comparison	Conventional treatment
Outcome	Dyspnea, pulmonary stasis, peripheral edema and angina were measured before and after 15 and 45 days of treatment. Electrocardiogram (ECG) performed before and after 15 days of treatment to assess variations in rhythm, type and number of premature beats, ST segment, T wave, and atrioventricular conduction
Study Design	Parallel randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Kuethe 2006	
Study Title	Creatine supplementation improves muscle strength in patients with congestive heart failure
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Patients with a history of congestive heart failure of more than 6 months, NYHA II and III, and a peak oxygen uptake (peak VO2) of less than 20 ml/min/kg be free from diseases limiting physical performance other than heart failure, e.g. peripheral artery disease.
Intervention	5 g creatine, four times daily. After 6 weeks patients were crossed over to the placebo group.
Comparison	Placebo, four times daily. After 6 weeks patients were crossed over to creatine group (5 g creatine)
Outcome	At baseline, after 6, and after 12 weeks, Cardiopulmonary exercise tests: Oxygen uptake (VO_2), carbon dioxide output (VCO_2), instantaneous expiratory gas concentration throughout the respiratory cycle, and minute ventilation (V_E), Peak oxygen uptake (Peak VO_2) . Six minute walk test: dyspnea, Minnesota living with heart failure questionnaire, Elbow flexor muscle strength and Echocardiography
Study Design	Cross over Randomised Control Trial
Country	Germany
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Ruda 1988	
Study Title	Reduction of ventricular arrhythmias by phosphocreatine (Neoton) in patients with acute myocardial infarction(177)

Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Patients aged 35 to 70 years(mean 56.0 f 1.5) with acute myocardial infaction (AMI) admitted to the coronary care unit within 6 hours of the onset of chest pain.
Intervention	CrP 2 g bolus injection followed by 2-hour infusion at the rate of 4g/h, a total of 10 gram. Patients also received morphine for pain relief
Comparison	Sodium chloride isotonic solution according to the PCr administration regimen. Patients also received morphine for pain relief
Outcome	Multiform ventricular premature beats (VPBs), Heart rate, Ventricular premature beats, ventricular arrhythmias, Ventricular tachycardia, Ventricular fibrillation. Complications/side
Study Design	Parallel randomised Control Trial
Country	Russia
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Cochrane Review title (Accession number): Cinnamon for diabetes mellitus (CD007170) (108)	
Akilen 2010	
Study Title	Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. (137)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Adults; aged ≥ 18 years; diagnosed with type 2 diabetes mellitus on two consecutive FPG measurements of greater than 7 mmol⁄ l; an HbA1c ‡ 7%;treated with oral hypoglycaemic agents.

Intervention	oral, cinnamon (C. cassia) capsule, 500 mg (1 x 500 mg) with breakfast, 1000 mg (2 x 500 mg) with lunch and 500 mg (1 x 500 mg) with dinner for 12 weeks
Comparison	oral, starch capsule, 500 mg (1 x 500 mg) with breakfast, 1000 mg (2 x 500 mg) with lunch and 500 mg (1 x 500 mg) with dinner for 12 weeks
Outcome	Height, weight and waist circumference (anthropometrics) were measured at baseline (week 0) and post-intervention (week 12) and BMI was calculated accordingly HbA1c; diastolic and systolic blood pressure; total cholesterol; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; triglycerides; FBGL; total energy intake; BMI
Study Design	Parallel randomised Control Trial
Country	United Kingdom
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	Thames Valley University UK; Jeffrey Kelson Diabetes and Endocrine Centre, Central Middlesex Hospital London; Brent NHS London; Department of Dietetics, Brent National Health Services, London; Research and Development Office,
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Altschuler 2007	
Study Title	The effect of cinnamon on A1c among adolescents with type 1 diabetes.(138)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Male and female adolescents aged 13 to 18 years diagnosed with type 1 diabetes mellitus > 18 months duration; presentation to the clinic for routine care, no hospital admissions for medical or psychiatric reasons

	in the 12 months before enrollment, ability to be accessed by phone and not pregnant.
Intervention	oral, cinnamon 1000 mg tablet, daily for 12 weeks
Comparison	oral, lactose tablet, daily for 12 weeks
Outcome	Primary outcome(s) HbA1c , daily insulin intake, adverse events, insulin sensitivity
Study Design	Parallel randomised Control Trial
Country	United States of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Kaminsky Family Fund, the President'sOffice,and the Senior Fellows program at Dartmouth College
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsor

Blevins 2007	
Study Title	Effect of cinnamon on glucose and lipid levels in non-insulin-dependent type 2 diabetes.(139)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Male and female participants with type 2 diabetes mellitus; no age limit Exclusion criteria: insulin use; cinnamon supplementation; HbA1c <6.0%; acute illness Diagnostic criteria: American Diabetes Association (2003) criteria Co-morbidities: not stated Co-medications: oral hypoglycaemic agents (metformin; thiazolidinediones); HMGCoA reductase inhibitors duration of diabetes
Intervention	oral, cinnamon (C. cassia) 500 mg capsule, twice a day for 3 months (12 weeks)
Comparison	oral, wheat flour capsule, twice a day, for 3 months (12 weeks)
Outcome	HbA1c measured at baseline and three months follow up

	FBGL, serum cholesterol triglyceride, serum insulin; BMI measured at 1,2 and 3 months follow up.
Study Design	Parallel randomised Control Trial
Country	United states of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	National Center for Research Resources, National Institutes of Health.
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsor
Crawford 2009	
Study Title	Effectiveness of cinnamon for lowering hemglobin A1c in patients with type 2 diabetes: a randomised, controlled trial(140)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Patients ≥ 18 years were recruited from the population served by the 96th Medical Group, Eglin Air Force Base,Florida. Patients were eligible if they were included in the Population Health database as patients with diabetes (International Classification of Diseases, 9th revision, code for diabetes), had an HbA1c of _7.0% on a laboratory blood draw during the last 6 months.
Intervention	Oral, 2 x 500 mg cinnamon (C. cassia) capsules, daily , 90 days (12.9 weeks).Co-interventions: food and normal medication
Comparison	Usual care, 90 days (12.9 weeks). Co-interventions: food and normal medication
Outcome	HbA1C at baseline and end of follow up
Study Design	Parallel randomised Control Trial
Country	United states of America
COI disclosed	Yes
Financial sponsor disclosed	Yes

Name of Financial sponsor	United States Air Force Surgeon General's Office for Population Health Research
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Khan 2003	
Study Title	Cinnamon improves glucose and lipids of people with type 2 diabetes(142)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Men and women with type 2 diabetes age >40 years, not on insulin therapy, not taking medicine for other health conditions, and fasting blood glucose levels between 7.8 and 22.2 mmol/l (140–400 mg/dl).
Intervention	(route, total dose/day, frequency): oral, 1 g (2 x 500 mg), 3 g (6 x 500 mg) or 6 g (12 x 500 mg) cinnamon (C. cassia) capsules, daily (3 groups) for 40 days (5.7 weeks). Co-intervention: sulfonylurea drugs, i.e., glibenclamide; medications did not change during the study.
Comparison	Placebo ;(route, total dose/day, frequency): oral, 2, 6 or 12 wheat flour capsules, daily (3 groups) for 40 days (5.7 weeks). Co-intervention: sulfonylurea drugs, i.e., glibenclamide; medications did not change during the study.
Outcome	On days 0, 20, 40, and 60 FBGL; fasting serum triglyceride; fasting serum cholesterol; fasting serum high-density lipoprotein cholesterol; fasting serum low-density lipoprotein cholesterol, VLDL, and LDL
Study Design	Parallel randomised Control Trial
Country	Pakistan
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	partly funded by University Grants Commission/NWFP Agricultural University, Peshawar, Pakistan

Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor
Khan 2010	
Study Title	Cinnamon may reduce glucose, lipid and cholesterol level in type 2 diabetic individuals(141)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Male and female diabetic patients , age≤40 years, with blood sugar levels ≥ 125 mg/dl, and not on insulin therapy
Intervention	Intervention (route, total dose/day, frequency): oral, 1.5 g (3 x 500 mg) cinnamon capsules, daily for 30 days
Comparison	Control (route, total dose/day, frequency): oral, 1.5 g (3 x 500 mg) maize flour capsules, daily for 30 days
Outcome	FBGL; fasting serum triglycerides; fasting serum cholesterol; fasting serum high-density lipoprotein cholesterol; fasting serum low-density lipoprotein cholesterol at day 0 and day 30
Study Design	Parallel randomised Control Trial
Country	Pakistan
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA
Mang 2006	
Study Title	Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes mellitus type 2(143)

Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Patients diagnosed with diabetes mellitus type 2 .Only patients treated with oral ant diabetics or diet were included in the study.
Intervention	(route, total dose/day, frequency): oral, cinnamon (aqueous extract of C.cassia) 1000 mg capsule, 3 times a day for 4 months (16 weeks)
Comparison	(route, total dose/day, frequency): oral, 1 microcrystalline cellulose (placebo) capsule, 3 times a day for 4 months (16 weeks)
Outcome	HbA1c; FBGL; total cholesterol; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; triacylglycerol measured at baseline and 4 months follow up
Study Design	Parallel randomised Control Trial
Country	Germany
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Truw Arzneimittel GmbH (Gütersloh, Germany) and Finzelberg GmbH & Co. KG (Andernach, Germany)
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Rosado 2010	
Study Title	A Study to Determine the Effects of Cinnamon on Blood Glucose and Lipid Levels in Persons with type-2 Diabetes [dissertation] (136)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Participants: Male and females aged 30 to 70 years; diagnosed with type 2 diabetes mellitus; taking metformin for glucose control for at least 3 months (at a daily dose of at least 1000 mg); and FBGL 7 0 to 16.7 mmol/L or HbA1c > 7%, with or without hyperlipidemia

Intervention	(route, total dose/day, frequency): oral, cinnamon 250 mg (water-soluble extract of C. burmanii; Cinnulin PF®) capsule, twice a day , for 40 days
Comparison	Placebo; Control (route, total dose/day, frequency): oral, 250 mg bran cereal (control) capsule, twice a day. For 40 days (5.7 weeks). Co-medications: metformin, hypolipidaemic agents, and any other prescribed medications
Outcome	HbA1c; FBGL, PPG, total cholesterol; triglycerides; low density lipoprotein cholesterol; high-density lipoprotein cholesterol Co-medications: metformin, hypolipidaemic agents, and any other prescribed medications
Study Design	Parallel randomised Control Trial
Country	Unites States of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Trippler Army Medical Center, Intergrity Nutreceuticals International and US Department of Agriculture
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	Rosado received ARCS foundation financial award, Soroptimist international foundation, US Army CORPS assosiaciton and Dr Hans and Clara Zimmerman foundation
Author's conclusions	Unfavourable to financial sponsor and author-financial sponsor financial ties

Suppapitiporn 2006	
Study Title	The effect of cinnamon cassia powder in type 2 diabetes mellitus(144)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Males and females, aged 30 to 70 years; diagnosed with type 2 diabetes mellitus (FBGL 120 to 180 mg/dL (6. 67 to 10.0 mmol/L); HbA1c > 7%); maintained a fixed dose of hypoglycaemic medication over the past 3 months;

Intervention	Oral, cinnamon (C. cassia) 1500 mg capsule, 3 times a day for 4 months (16 weeks)
Comparison	Oral, 1 placebo capsule, 3 times a day for 4 months (16 weeks)
Outcome	HbA1c; FBGL; total cholesterol; triglyceride; high-density lipoprotein cholesterol; creatinine; serum glutamic oxaloacetic transaminase; serum glutamic pyruvic transaminase; blood urea nitrogen; body weight; blood pressure measured at baseline and at 4 months follow-up
Study Design	Parallel randomised Control Trial
Country	Thailand
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Vanschoonbeek 2006	
Study Title	Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients(145)
Non-communicable disease	Diabetes
Nutrition-related risk factor	NA
Population	Postmenopausal women diagnosed with type 2 diabetes mellitus
Intervention	oral, cinnamon 500 mg (C. cassia) capsule, 3 times a day for 6 weeks
Comparison	oral, 1 wheat flour capsule, 3 times a day for 6 weeks
Outcome	HbA1c; FBGL; fasting plasma insulin; OGIS; ISIcomp; HOMA-IR; total cholesterol; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; triacylglycerol tests before and after follow up
Study Design	Parallel randomised Control Trial
Country	Netherlands
COI disclosed	No
Financial sponsor disclosed	No

Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Cochrane Review title (Accession number): Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients (CD007653) (85)	
Auer 1990	
Study Title	Hypertension and hyperlipidaemia: garlic helps in mild cases(178)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Non-hospitalized patients, recruited from general practices, with mild hypertension (WHO stage I and II, diastolic pressure between 95-104 mmHg on "two control measurements with 14 days between each.
Intervention	Fourteen days of "acclimatisation" then followed by active treatment 100mg each garlic powered preparation three times daily for 12 weeks
Comparison	14 days of"acclimatization" followed by two capsules of a similar looking placebo three times daily for 12 weeks
Outcome	Pulse, triglycerides, total cholesterol, supine/standing systolic and diastolic blood pressure, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, and blood sugar, serum glutamate pyruvate transfarase, serum glutamate oxaloacetate transaminase, and blood sugar at week 0,4,8 and 12.
Study Design	Multicentre randomised Control Trial
Country	Germany
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No

Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Cochrane Review title (Accession number): Coenzyme Q10 for heart failure (CD008684) (89)	
Adarsh 2008	
Study Title	Coenzyme Q10 (CoQ10) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM)(162)
Non-communicable disease	Cardiovascular Diseases
Nutrition-related risk factor	NA
Population	Men and women ages 24 to 75 years, with hypertrophic cardiomyopathy (HCM) diagnosed clinically and by echocardiography and NYHA II class of Heart Failure with symptoms of palpitation/dyspnea /chest pain and /or presyncope /syncope and echocardiographic proven diagnosis were taken up for the study.
Intervention	100 mg of coQ10 twice daily in addition to conventional therapy for 12 weeks
Comparison	Conventional treatment without CoQ10 for 12 weeks
Outcome	Symptoms improvement (NYHA classification) Quality of life on detailed questionnaire and on 6-minute walk test Mortality Improvement in diastolic dysfunction Improvement in mitral regurgitation Reduction in LVOT gradient in obstructive cases
Study Design	Non Randomised Control Trial
Country	India
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA
Berman 2004	

Study Title	Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study(163)
Non-communicable disease	Cardiovascular Diseases
Nutrition-related risk factor	NA
Population	Men and women patients aged> 18 years, with end-stage heart failure awaiting heart transplantation. Inclusion criteria were NYHA functional class 3 or 4, left ventricular ejection fraction < 25%, cardiopulmonary exercise test (CARPET) with maximal O2 consumption < 14 ml/kg/h, and evident symptoms of heart failure such as nocturia, dyspnea, and paroxysmal nocturnal dyspnea.
Intervention	Ultrasome™—CoQ10 (special preparation to increase intestinal absorption) twice daily for 3 months
Comparison	Corn flour-based placebo for three months
Outcome	Symptoms improvement (NYHA classification) ,symptoms improvement measured on the Minnesota Living with Heart Failure Questionnaire, Quality of life on 6-minute walk test ,Blood tests for atrial natriuretic factor (ANP) and alpha *Tumor necrosis factor alpha* (TNF), Echocardiography. Six weeks into the trial, CoQ10 blood levels were measured to assess absorption and compliance
Study Design	Parallel randomised Control Trial
Country	Israel
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Keogh 2003	
Study Title	Randomised double-blind, placebo controlled trial of coenzyme Q10 therapy in class II and III systolic heart failure.(164)
Non-communicable disease	Cardiovascular Diseases

Nutrition-related risk factor	NA
Population	Patients aged 18 to 80 years with NYHA class II or III heart failure Patients were and had Class II or III heart failure symptoms due to ischaemic, valvular or idiopathic dilated cardiomyopathy with left ventricular systolic impairment (ejection fraction < 0.4).
Intervention	150 mg/day coenzyme Q10 (3 divided doses); low-fat dietary advice with conventional medicine
Comparison	placebo (3 divided doses); low-fat dietary advice with conventional medicine
Outcome	Symptom class by NYHA and SAS Exercise tolerance by a 6-minute walk test Walk test and treadmill exercise test (modified Naughton stress test) assessment for clinical outcomes of heart failure Plasma levels of coenzyme Q10, Assessment for the clinical outcomes of heart failure including readmission, transplantation or death, serum creatinine, sodium and potassium
Study Design	Parallel randomised Control Trial
Country	Australia
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Blackmores Ltd, Balgowlah, Sydney, and Pharma Nord, Denmark
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Khatta 2000	
Study Title	The effect of coenzyme Q10 in patients with congestive heart failure(165)
Non-communicable disease	Cardiovascular Diseases
Nutrition-related risk factor	NA
Population	Adults patients ages > 18 years with congestive heart failure with NYHA class III and IV symptoms.
Intervention	200 mg/day of CoQ10 for a period of 6 months

Comparison	Placebo for a period of 6 months
Outcome	Baseline and after 6 weeks: a graded symptom-limited cardiopulmonary exercise test using the Naughton protocol, Radionuclide ventriculography was performed by using standard techniques and Serum concentration of coenzyme Q_{10} was measured.
Study Design	Parallel randomised Control Trial
Country	United States of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	grant P60AG12583 from the National Institute of Aging, Claude D. Pepper Older Americans Independence Center, Bethesda, Maryland
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsor

Kocharian 2009	
Study Title	Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy.(166)
Non-communicable disease	Cardiovascular Diseases
Nutrition-related risk factor	NA
Population	Patients younger than 18 years with a complete profile as a known case of idiopathic dilated cardiomyopathy according to the definition of World Health Organization classification with stability of at least 1 month in medications, received for treatment of cardiac failure and with presence of a normal sinus rhythm.
Intervention	coenzyme Q10 2 mg/kg/day in 2 or 3 divided doses, these being increased to the maximum dose of 10 mg/kg/day according to tolerance or the appearance of side effects with conventional medicine
Comparison	placebo in 2 or 3 divided doses per day with conventional medicine
Outcome	Left ventricular ejection fraction

Study Design	Parallel randomised Control Trial
Country	Iran
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Morisco 1993	
Study Title	Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study(167)
Non-communicable disease	Cardiovascular Diseases
Nutrition-related risk factor	NA
Population	Adults Patients ages > 18 years with NYHA III or IV heart failure Patients affected by severe congestive heart failure, as assessed by history of heart disease with symptoms of dyspnea or fatigue or both together with signs of fluid retention, and no evidence of primary pulmonary disease.
Intervention	coenzyme Q10 50 mg twice or 3 times daily
Comparison	Placebo twice or 3 times daily
Outcome	NYHA clinical status Incidence of severe cardiovascular complications (pulmonary oedema, cardiac asthma, arrhythmia), Length of hospitalisation
Study Design	Multicenter randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Associazione Italiana per la Ricerca in Medicina Interna (AIRMI)
Author-financial sponsor ties disclosed	No

Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Munkholm 1999	
Study Title	Coenzyme Q10 treatment in serious heart failure(168)
Non-communicable disease	Cardiovascular Diseases
Nutrition-related risk factor	NA
Population	Adults > 18 years with NYHA II or III heart failure with stable heart values of LVIDD and LVEF on two echocardiographic examinations spaced 3 months apart differed by less than 5%, and unchanged medication in that period.
Intervention	coenzyme Q10 in soya oil 100 mg twice daily for 12 weeks
Comparison	placebo-capsules containing only soya oil ,twice daily for 12 weeks
Outcome	Baseline and post-therapeutic serum levels of coenzyme Q10 ,Left ventricular ejection fraction and NYHA clinical status
Study Design	Parallel randomised Control Trial
Country	Denmark
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Cochrane Review title (Accession number): Dietary flavonoid for preventing colorectal neoplasms (CD009350) (32)	
Akhter 2008	
Study Title	Dietary Soy and Isoflavone Intake and Risk of Colorectal Cancer in the Japan Public Health Center Based Prospective Study.(128)
Non-communicable disease	Cancer

Nutrition-related risk factor	NA
Population	Japanese nationals ages 45 -74 years visiting public health centres.
Intervention (Exposure)	Dietary soy and isoflavone intake
Comparison	NA
Outcome	Association of isoflavone intake with CRC risk and Adjusted for age, public health centre area, history of diabetes mellitus, BMI, leisure time physical activity, smoking, alcohol, intake of vitamin D, dairy products, meat, vegetable, fruit, and fish, also adjusted for menopausal status and current use of female hormones in women
Study Design	Prospective Cohort Study
Country	Japan
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	Grant-in-Aid for Cancer Research and for the Third-term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	M Akhter received a Research Resident Fellowship from the Foundation forPromotion of Cancer Research (Japan) for the Third-term Comprehensive 10-Year-Strategy for Cancer Control.
Author's conclusions	Unfavourable to financial sponsor and author-financial sponsor ties

Akhter 2009	
Study Title	Dietary isoflavone and the risk of colorectal adenoma: a case-control study in Japan(129)
Non-communicable disease	Cancer
Nutrition-related risk factor	NA
Population	Men aged 50–79 years or women aged 40–79 years who underwent total colonoscopy from the anus to the caecum.
Intervention (Exposure)	Isoflavone intake
Comparison	NA
Outcome	Association of isoflavone intake with CRC risk adjusted for age, public health centre area, history of diabetes mellitus, BMI, leisure time

	physical activity , smoking, alcohol, intake of vitamin D, dairy products, meat, vegetable, fruit, and fish, also adjusted for menopausal status and current use of female hormones in women
Study Design	Case control Study
Country	Japan
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	Comprehensive 10-year Strategy for Cancer Control from the Ministry of Grants-in-Aid for Cancer Research (17-9) and for the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan, and by Grants-in-Aid for Scientific Research on Priority Areas (17015049) and for Young Scientists (A-19689014) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	M Akhter received a Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the Third-term Comprehensive 10-year Strategy for Cancer Control.
Author's conclusions	Favourable to financial sponsor and author-financial sponsor ties
Bobe 2008	
Study Title	Dietary flavonoids and colorectal adenoma recurrence in the Polyp Prevention Trial(130)
Non-communicable disease	Cancer
Nutrition-related risk factor	NA
Population	Participants at least 35 years of age and have had at least one histologic confirmed colorectal adenoma identified in six months before study entry (I = 958, C = 947); had to be within 150% of their recommended weight, without a history of inflammatory bowel disease, bowel resection, adenomatous polyposis syndrome, or prior history of adenomas or CRC, and not currently using lipid-lowering medications

Intervention	Intake of total flavonoids, 6 major flavonoid subgroups, and 29 individual flavonoids by intake of low-fat high-fiber, high-fruit, and high-vegetable diet
Comparison	NA
Outcome	Association of total flavonoids and six main flavonoid subgroups intake with adenoma recurrence Adjusted for age, sex, BMI, dietary fibre consumption, and regular NSAID use.
Study Design	Randomized, multicenter trial
Country	United States of America
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	Intramural Research Program, National Cancer Institute, NIH, Bethesda, MD
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Cutler 2008	
Study Title	Dietary flavonoid intake and risk of cancer in postmenopausal women: the Iowa Women's Health Study(131)
Non-communicable disease	Cancer
Nutrition-related risk factor	NA
Population	Post-menopausal women, aged between 55-69 years randomly selected
Intervention (Exposure)	Flavonoid intake
Comparison	NA
Outcome	Association of total flavonoids and seven flavonoid subclasses with lung, colorectal, breast, pancreatic and upper aerodigestive cancer risk among postmenopausal women. Adjusted for age, energy intake , education level, race, BMI, multivitamin use, activity, smoking history and pack years

Study Design	Prospective Cohort study
Country	United States of America
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	National Cancer Institute and International Life Sciences Institute (ILSI)
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Lin 2006	
Study Title	Flavonoid intake and colorectal cancer risk in men and women (132)
Non-communicable disease	Cancer
Nutrition-related risk factor	NA
Population	Female registered nurses aged 30–55 years from 11 US states and US male dentists, podiatrists, pharmacists, optometrists, osteopaths and veterinarians aged 40–75 years were enrolled.
Intervention(exposure)	Total intake and intake of individual flavonoids
Comparison	NA
Outcome	Association of total flavonoids and three flavonoid subclasses intake with CRC risk adjusted for age, BMI, family history of CRC, history of colorectal polyps, prior sigmoidoscopy screening, physical activity, smoking, red meat intake, alcohol , total energy, calcium, folate and fibre intake, aspirin and multivitamin use, and postmenopausal hormone replacement therapy in women
Study Design	Prospective Cohort Study
Country	United States of America
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	National Institutes of Health and National Colorectal Cancer Research Alliance

Author-financial sponsor ties disclosed	Yes Dr. Jennifer Lin is a recipient of a National Cancer Institute Career Development Award (KCA112529).
Name of Author-financial sponsor ties	National Cancer Institute Career Development Award (KCA112529).
Author's conclusions	Unfavourable to financial sponsor and author-financial sponsor ties

Simons 2009	
Study Title	Dietary flavonol, flavone and catechin intake and risk of colorectal cancer in the Netherlands Cohort Study(133).
Non-communicable disease	Cancer
Nutrition-related risk factor	NA
Population	Men and women aged 55–69 years
Intervention (Exposure)	Intake of total flavonoids and three flavonoid subclasses
Comparison	NA
Outcome	Association of flavonol, flavone and catechin intake with CRC risk Adjusted for age, family history ofCRC, smoking, alcohol, occupational physical activity at longest held job, BMI and processed meat intake
Study Design	Prospective Cohort Study
Country	Netherlands
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Dutch Cancer Society, Netherlands Organization for Scientific Research–Earth and Life Sciences (NWO-ALW) (VENI Innovational Research Grant to ICWA).
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsors

Theodoratou 2007	
Study Title	Dietary flavonoids and the risk of colorectal cancer(134)
Non-communicable disease	Cancer

Nutrition-related risk factor	NA
Population	Men and women aged 16 to 79 years with incident cases of adenocarcinoma of colon or rectum in patients presenting to surgical units in Scottish hospitals
Exposure	Dietary flavonoids intake
Comparison	NA
Outcome	Association of six main flavonoid subclasses intake with CRC risk Adjusted for family history of CRC, total energy intake, total fibre intake, alcohol intake, NSAID intake, smoking, BMI, physical activity mutually between flavonoid categories
Study Design	Case control Study
Country	Scotland
COI disclosed	No
Financial sponsor disclosed	Yes
Name of Financial sponsor	Medical Research Council, Chief Scientist Office, and Cancer Research UK
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	Medical Research Council, Chief Scientist Office, and Cancer Research UK,(M. Dunlop, H. Campbell, and M. Porteous) and Greek State Scholarship Foundation, studentship (E. Theodoratou).
Author's conclusions	Favourable to financial sponsor and author-financial sponsor ties

Wang 2009	
Study Title	Dietary intake of selected flavonols, flavones, and flavonoid-rich foods and risk of cancer in middle-aged and older women(135)
Non-communicable disease	Cancer
Nutrition-related risk factor	NA
Population	Women aged ≥ 45 years
Intervention (Exposure)	Intake of selected flavonoids and flavonoid-rich foods
Comparison	NA
Outcome	Association of flavonoids intake with breast, colorectal, lung, endometrial and ovarian cancer risk Adjusted for smoking , alcohol, physical activity, postmenopausal status, hormone replacement

	therapy use, multivitamin use, BMI, family history of CRC, ovary cancer, and breast cancer, intake of fruit and vegetables, fibre, folate and saturated fat, and history of benign colorectal polyps
Study Design	Prospective Cohort Study
Country	United States of America
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	National Institutes of Health, Bethesda, MD, Research Scholar Grant from the American Cancer Society and US Department of Agriculture Research Service.
Author-financial sponsor ties disclosed	Yes
Name of Author-financial sponsor ties	MD; a Research Scholar Grant from the American Cancer Society; and US Department of Agriculture. Research Service under Cooperative Agreement no. 58-1950-4-401
Author's conclusions	Unfavourable to financial sponsor and author-financial sponsor ties

Cochrane Review title (Accession number): Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease (CD010405) (96)	
Bargossi 1994	
Study Title	Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors(169)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	34 outpatients with primary hypercholesterolaemia (LDL-cholesterol > 190 mg/dl, triglycerides < 200 mg/dl, 5 ° percentile < HDL-cholesterol < 95 ° percentile of a reference population recruited in Italy
Intervention	Drug-free controlled diet period followed by (statin + CoQ10): simvastatin (20 mg/day) plus CoQ10 (100 mg/day) for 3 months, followed by crossover to control
Comparison	Drug-free controlled diet period followed by Control (statin): simvastatin (20 mg/day) for 3 months After this first 3-month (90-day)

	phase the 2 groups were crossed over followed by crossover to intervention
Outcome	Blood pressure, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides
Study Design	Cross over Randomised Control Trial
Country	Italy
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA
Kaikkonen 2000	
Study Title	Antioxidative efficacy of parallel and combined supplementation with coenzyme Q10 and d-α-tocopherol in mildly hypercholesterolemic subjects: a randomised placebo controlled clinical study(170)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Men and postmenopausal women, aged 60.7±5.7 years, with body mass index 26.9 :k 3.6 kg/m 2 (mean + SD), mild hypercholesterolemia (serum cholesterol 5.90 i 0.96 mmol/1, mean ± SD) and a regular HMG-CoA reductase inhibitor treatment.
Intervention	Intervention (CoQ10): Soy bean oil-based CoQ10 (2 x 100 mg daily) for 3 months. 2 capsules in the morning and 2 in the evening with meals Co-intervention: conventional treatments and lifestyle.
Comparison	Soybean oil capsules, 2 capsules in the morning and 2 in the evening with meals. Co-intervention: conventional treatments and lifestyle.
Outcome	Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides
Study Design	Parallel randomised Control Trial
Country	Finland
COI disclosed	No

Financial sponsor disclosed	Yes
Name of Financial sponsor	Pharma Nord, Denmark and the Yrj6 Jahnsson Foundation, Finland.
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsor

Lee 2011	
Study Title	Effects of coenzyme Q10 on arterial stiffness, metabolic parameters, and fatigue in obese subjects: a double-blind randomised controlled study(171)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Obese men and women with age>20 years of age, BMI greater than 25 kg/m2
Intervention	200 mg CoQ10 pill once a day for 12 weeks
Comparison	placebo pill once a day for 12 weeks
Outcome	Systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides
Study Design	Parallel randomised Control Trial
Country	Korea
COI disclosed	Yes
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Mabuchi 2007

Study Title	Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study(160)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Japanese men and women with hypercholesteraemic (above 220 mg/dL).
Intervention	4-week dietary lead-in period (less than 300 mg/day of low cholesterol diet) followed by (statin + CoQ10): atorvastatin (10 mg/day) for 16 weeks plus CoQ10 (100 mg/day) for 12 weeks with no changes to dietary and smoking patterns.
Comparison	4-week dietary lead-in period (less than 300 mg/day of low cholesterol diet) followed by Control (statin + placebo): atorvastatin (10 mg/day) for 16 weeks plus placebo for 12 weeks with no changes to dietary and smoking patterns
Outcome	Serum total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides
Study Design	Parallel randomised Control Trial
Country	Japan
COI disclosed	Yes
Financial sponsor disclosed	Yes
Name of Financial sponsor	Kaneka Co.
Author-financial sponsor ties disclosed	No check
Name of Author-financial sponsor ties	NA
Author's conclusions	Favourable to financial sponsor

Yamagami 1986	
Study Title	Effect of coenzyme Q10 on essential hypertension, a double blind controlled study. Biomedical and Clinical Aspects of Coenzyme Q10(161)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA

Population	Men and women with essential hypertension whose blood pressure was higher than 150/90 mmHg
Intervention	Lead-in period of at least 4 weeks, during which symptoms and blood pressure were stable followed by 3 capsules daily 33.3 mg CoQ10 daily
Comparison	Lead-in period of at least 4 weeks, during which symptoms and blood pressure were stable followed by 3 capsules daily of inactive placebo.
Outcome	Systolic blood pressure, diastolic blood pressure
Study Design	Parallel randomised Control Trial
Country	Japan
COI disclosed	No
Financial sponsor disclosed	No
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	NA

Young 2007	
Study Title	Effect of coenzyme Q10 supplementation on simvastatin-induced myalgia(172)
Non-communicable disease	Cardiovascular Disease
Nutrition-related risk factor	NA
Population	Male and female patients with previous statin-related myalgia
Intervention	2-week washout of coenzyme Q10 supplements and lipid-modifying therapies, except for ezetimibe followed CoQ10 capsules (200 mg/day) for 12 weeks combination with upward dose titration of simvastatin from 10 mg/day, doubling every 4 weeks if tolerated to a maximum of 40 mg/ day.
Comparison	2-week washout of coenzyme Q10 supplements and lipid-modifying therapies followed by placebo for 12 weeks in combination with upward dose titration of simvastatin from 10 mg/day, doubling every 4 weeks if tolerated to a maximum of 40 mg/day
Outcome	Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides

Study Design	Parallel randomised Control Trial
Country	New Zealand
COI disclosed	Yes
Financial sponsor disclosed	National Heart Foundation of New Zealand, Auckland , New Zealand
Name of Financial sponsor	NA
Author-financial sponsor ties disclosed	No
Name of Author-financial sponsor ties	NA
Author's conclusions	Unfavourable to financial sponsor

Table a8: Table of excluded primary studies

	Title of Primary Study	Reason for exclusion
Pedone 1984	**An assessment of the activity of creatine phosphate (Neoton) on premature ventricular beats by continuous ECG monitoring in patients with coronary cardiac disease.** (189)	Article was published in a language other than English
Pedone 1984-2	**Myocardial T1-201 scintigraphy in the study of the development of acute myocardial infarction. Evaluation of the effects of a drug with metabolic action: creatine phosphate.** (190)	Article was published in a language other than English
Samarenko 1987	**Initial experience with using phosphocreatine in patients in the early (up to 6 hours) period of myocardial infarction.** (191)	Article was published in a language other than English
Zahorska-Markiewicz	**Effect of chitosan in complex management of obesity.** (192)	Article was published in a language other than English
Carmenini 1994	**Controlled multicentric clinical study with placebo in patients with dilatative myocardiopathy functional class II-III N.Y.H.A. treated with oral phosphocreatinine.** (193)	Article was published in a language other than English
Maggi 1990	**Double-blind multicenter clinical trial on the efficacy of phosphocreatinine vs L-carnitine and placebo in a group of patients affected by heart disease.** (194)	Article was published in a language other than English
Zochowski 1994	**Use of phosphocreatinine in treatment of acute heart failure.** (195)	Article was published in a language other than English
Kandadziora 1988	**Blood pressure and lipid lowering effect of garlic preparations in combination with a diuretic.** 196)	Article was published in a language other than English

Table A8 is a list of the primary studies included in Cochrane nutrition reviews addressing alternative nutrition supplements and the four major NCDs and their nutrition-related risk factors which did not meet the inclusion criteria for selecting primary studies. The primary studies were excluded as they were published languages other than English.

Table a9: Research Gaps for Cochrane nutrition reviews addressing cancer

Table a9 shows the detailed summary of the research gaps identified in the "implications for research" section of Cochrane nutrition reviews addressing cancer. The first column (NCD grouping) is the NCD grouping being addressed i.e. cancer. The second column (Domain) is the EPICOT+ Framework item i.e. population, intervention, comparison, outcome, study design and time frame. The third column is the research recommendation for which future research should address e.g. children. The number in the brackets e.g. (44, 45) is the citation of review(s) (found in the References list (Section 7)) which have made that particular future recommendation. The fourth column (Example) is an example of the text from the "implications for research" section from which we identified the research gaps.

NCD Grouping	Domain	Future research recommendations	Example
Cancer	Population	• Children (41,45) • Women (46) • Young people (31,45) • Men (31) • Non-Chinese population (44) • Individuals at risk of cancer (39) (41) (31) • Carers of people with cancer (45) • Individuals with different types of cancer (43) (42) • Homogeneous study populations (anticancer treatment received, disease stage) (41,47) (44)	Future trials should be RCTs performed in homogeneous study populations (e.g. with regards to anticancer treatment received) (47)

	• Subgroups with baseline selenium exposure levels and genetic factors (46)	
Intervention	**Supplementation** • EPA (43) • Sodium selenite (50) • Nutritional support (45) • Lycopene (51) • Vitamin D (31) • Calcium (39) **Other** • Exclude other supportive therapies (43) • Different dosage of intervention (32,39,40,49,50) • Different species of intervention (32,43,46,48) • Objective assessment of interventions (48) • Intervention combined with complementary medicine (41,46) • Different modalities of feeding (42)	Future trials should aim for the intervention group to have that level of intake (30 to 40 mg per day of fibre) and preferably higher 49).
Comparison	• Placebo (32,43)	There is need to conduct good quality large scale randomised controlled trials using EPA compared to placebo with different cancer types (43).
Outcomes	• Survival (41,43,44) • Mortality (51) • Diagnosis of cancer (46) (51) • Adverse effects and/or events (41)	Future trials on the use of retinoic acid (either with or without other treatments like anti-GD2) after autologous stem

		• Safety of intervention (45) • Efficacy of intervention (31,44,45,48,51) • Quality of life (31,41) • PSA levels (51) • Preferred endpoint of Colorectal cancer (49) • Risk-benefit balance (39) • Valid definitions of outcomes (47) • Adopting standardised outcome measures (45)	cell transplant for children with high-risk neuroblastoma should be RCTs focusing on survival, (late) adverse effects, and quality of life (41).
	Study Design	<u>Design of Primary Study</u> • High quality RCTs(32,40,43–45,51) (31,41,47–50) • Adequately powered and/or larger RCTs (39–41,43,45,47) • Explicitly explaining of trial methodology (enrolment, sequence generation, allocation concealment, randomisation, blinding and ITT analysis (44) • Multicenter trials (39) • Non-experimental cohort studies (40) • Observational studies (46) • Adopting SPIRIT guidelines (31). <u>Reporting in Primary Study</u> • Adopting the CONSORT statement (31,43,48) • Standardised and consistent reporting of results (45)	There is need for a well-designed, high methodological quality, randomised controlled trial to investigate the effectiveness lycopene for the prevention of prostate cancer (51).

	Timeframe	• Long period of follow-up (40) (41) (31,49) • Long-term survival (44)	RCTs should be performed in homogeneous study populations (like stage of disease) and have a long-term follow-up (41)

Table a10: Research Gaps for Cochrane nutrition reviews addressing cardiovascular diseases

Table a10 shows the detailed summary of the research gaps identified in the "implications for research" section of Cochrane nutrition reviews addressing cardiovascular diseases. The first column (NCD grouping) is the NCD grouping being addressed i.e. cardiovascular diseases. The second column (Domain) is the EPICOT+ Framework item i.e. population, intervention, comparison, outcome, study design and time frame. The third column is the research recommendation for which future research should address e.g. women. The number in the brackets e.g. (64) is the citation of review(s) (found in the References list (Section 7)) which have made that particular future recommendation. The fourth column (Example) is an example of the text from the "implications for research" section from which we identified the research gaps.

NCD Grouping	Domain	Recommendation	Example
Cardiovascular Diseases	Population	• Early stages of life (95) • Women (92) • Healthy people (35) (86) • Groups other than middle-aged women (13) • Ethnicity (75) (69) (36) • Gender (78) (95) • Older people (69,95) • Individuals at risk of cardiovascular diseases (12) (84) (76) • Individuals with hypertension (90) (77,78,85,88) (73) • People with PAD (63) • People with post-stroke dysphagia (64) • Populations with low calcium intake (95)	More placebo controlled trials are warranted to clarify whether calcium supplementation can reduce blood pressure in people with elevated blood pressure (77)

		• Individuals with a previous cerebral haemorrhage (71) • Older patients (those aged over 80 years) stroke (71) • Individuals with acute states of COPD (66) • People with FH and their care givers (70) • Participants across a wider range of selenium status (92) • Poor people (69) • Socially excluded people (69) •	
Setting		• Primary care and the workplace compared with hospital settings (68) • population and community level (35) • United Kingdom healthcare and other settings (35) • lower and higher income countries (72) • low and middle-income countries (69). • Developing countries (69) • population level (e.g. workplace, institutional, regulatory) (91) • international setting (36)	Research in the setting in which dietary advice is given would inform us about the effectiveness of advice in primary care and the workplace compared with hospital settings (68)
Intervention	**Food**	• Effect of cocoa (90) • Higher content and /or better bioavailability of the active peptides (87) • Garlic therapy (62) • Effects of ALA (72) • Dietary fish (72) • Dose and formulation of omega-3 fatty acid (74) • Ranges of selenium concentration and dietary selenium intakes (92) • Provision of fruit and vegetables (13) • Black and green tea (94)	Long term research to help us understand what types of unsaturated fats are most useful in the diet when replacing saturated fats (monounsaturated fats, polyunsaturated fats and the relevant specific fatty acids) are urgently needed. (12)

- Garlic Dosage (85)
- Creatine analogues (83)
- Isoflavones (36)

Dietary patterns and advice

- Low-fat dietary intervention (86)
- Cholesterol-lowering diet (70)
- Whole grain diets (82)
- Low GI diets (76)
- Elements of dietary advice (e.g. length and frequency of contact, type of approach (e.g. individual or group, behavioural therapy or instructional techniques), level of belief of practitioner, level of training of practitioner, patient satisfaction, initial characteristics of patients (68)
- Types of unsaturated fats replacing saturated fats (12)
- Effect of dietary interventions (88)
- Maintenance of dietary fat modification whilst on lipid lowering medication (12)
- Reduced saturated fat whilst on lipid-lowering medication (10)
- Plausible interventions of dietary salt reduction (91)
- Effect of dietary calcium vs supplemental version (95)
- nurse-led dietary interventions compared with dietetic advice (68)

Nutritional education and counselling programmes

- Types of self-help resources (interactive computer programmes vs simple leaflets (68)
- Modality of administering self-help (leaflet handed out by a doctor vs nurse vs post) (68)
- Non-individualised modes of dietary health promotion (35)
- Weight-loss and maintenance program (84)
- Low sodium dietary advice and reduced sodium advice (73)
- Advice to consume more fruit and vegetables (13)

Policy

- Effects and costs of health protection (i.e.fiscaland legislative approaches) and primary prevention (69)
- Effectiveness of non-individualised modes of dietary health promotion (35)
- Effects of legislation (to alter fat contents of foods, improved labelling, pricing initiatives and improved availability of healthier(12)
- Voluntary and regulatory salt reduction by food industries (such as the UK's reduction of salt in processed foods) (91)

Supplementation

- Potassium supplementation (alone) (80) (79)
- Potassium &magnesium BP (80)
- Coenzyme Q10 (89,96)
- Calcium supplementation (77) (95)
- Vitamin E Dosage (65)
- Selenium supplements (92)
- Magnesium supplementation (78)

	• Daily calciumin intake of at least 1gm in comparison with a control group (95) **Other** • Sufficiently full details of the interventions (67) • Nature and duration of the intervention (93) • Equivalent attention and health professional time to participants (10) • Components of swallowing therapy (64) • Enhanced nutrition, anti-inflammatory nutrition supplements, exercise, vitamin D, anabolic agents, novel treatments such as selective androgen receptor modulators (SARMs), peroxisome proliferator-activated receptors (PPARs) agonists, neuro electric stimulation and specific anti-inflammatory medications (66) .	
Comparison	• Placebo (36,65,74,77–79,85) • Usual Care (86) • Vitamin E vs another treatment (65) • Cholesterol-lowering diet vs no dietary intervention(70) • Control group (95) • Dietary calcium vs supplemental version (95) • Daily calciumin take of at least 1gm in comparison with a control group.(95)	A three-arm or factorial trial comparing vitamin E to another treatment as well as to placebo would be useful (65)
Outcome	• Mortality (12,65,72,73,75,82,85,88,91) • Morbidity (73,85,88,91,91) • Adverse events (74,85,88,95,96) • Quality of life or health related quality of life (35,66,74,96) (64)	Trials utilising quality of life outcomes or cost-effectiveness evaluation are lacking (35)

	• Cardiovascular events (12,13,74,82,90,94,96). • Cardiovascular outcomes (72,76,77) • Cardiovascular disease risk factors (76) • Definition of cardiovascular events measures (36) • Vasoconstriction (95) • Number of participants who develop chest infection or pneumonia or who have signs of aspiration (64) • Blood pressure (72,77,81,91,95) • Long term effects on Blood pressure (80) • Diabetes risk (92) • Hormonal and lipid outcomes (91) (72,92) • Ankle brachial pressure index(ABI) (74) • Amputation rate (65) • Walking distance (74) • Time to healing (67) • Sustainability of behavioural change (13) • Skill level of staff providing care (67) • Need of vascular surgery (65) • Subjective and objective outcome measures (65) • Standardised outcome measures (64) • Legislation to modify fat (10) • Functional outcome (death or dependency)(64) • Length of inpatient stay and discharge to an institution (64) •	
Study Design	<u>Design of primary studies</u> • RCTs (12,13,35,62,65,66,69,70,73,75,77,79,80,85,86,88–92,94–96) • Multicentre trials (36,64,67,70,84,84)	Further large and high-quality trials of ALA carried out in lower and higher income countries

	• A three-arm or factorial trial (65) • High quality randomised controlled trials (6,31,35,36,64,67,68,72,76,78–80,82,84,91,125) • Larger trials or adequately powered (36,62,64,65,67,70,72,74,76–78,80,82–85,91,93,95) • Well-designed prospective population studies (75) • Economic evaluation/cost effectiveness studies (10,12,35,69,96) • Systematic reviews (10,84) • Qualitative studies (69,69) • Random sequence generation and treatment allocation (64,65,67,77–79,125) • Blinding (64,67,78,125) • Attrition (64) • ITT analysis (65,67,78,125,125) • Subgroup analysis (95) <u>Reporting in primary studies</u> • Adopting the CONSORT statement (67)	and that assess baseline ALA intake and use biomarkers to assess compliance would be helpful to clarify the cardiovascular effects of ALA. (40)
Time frame	• Long-term trials (12,13,36,75,88,90) (35,76) (84) (73) (91). (79) (86) (77) (10) (74) (82,95) • sufficient duration of length of follow-up (62) (67) (19) • Long-term follow-up data (88) • Long-term effect of weight loss on stroke incidence (84) • Long enough time span to detect any long term effects on BP (80) • long term effects of black and green tea interventions (94)	They should enrol a large number of participants and have long enough follow-up to allow detection of any meaningful long-term effects of magnesium supplementation (78).

Table a11: Research Gaps for Cochrane nutrition reviews addressing chronic respiratory diseases

Table a11 shows the detailed summary of the research gaps identified in the "implications for research" section of Cochrane nutrition reviews addressing chronic respiratory diseases. The first column (NCD grouping) is the NCD grouping being addressed i.e. chronic respiratory diseases. The second column (Domain) is the EPICOT+ Framework item i.e. population, intervention, comparison, outcome, study design and time frame. The third column is the research recommendation for which future research should address e.g. children. The number in the brackets e.g. (94-96) is the citation of review(s) (found in the References list (Section 7)) which have made that particular future recommendation. The fourth column (Example) is an example of the text from the "implications for research" section from which we identified the research gaps

NCD Grouping	Domain	Recommendation	Example
Chronic respiratory diseases	Population	• Children (57,59,60) • Adolescents (57) • Adults (59) • Birth and at least six years of follow up (61) • People with chronic asthma (52) • People with exercise induced bronchoconstriction/asthma (54,56) • Patients with different levels of asthma severity (58) • Habitual consumers and non-consumers of caffeine (58)	Further studies should examine whether weight reduction leads to asthma control in people with chronic asthma (52).
	Setting	• Low-income countries (e.g. Africa) (57)	There is also a need for these well designed studies in children and adolescents, as well as in low-income countries such as Africa (57)

Intervention	**Foods** • Caffeine ingestion (58) • Role of tartrazine and other food additives (55) • Effect of Mono and multifaceted inhalant and/or food allergen reduction (61) • **Dietary patterns and advice** • Effects of diet and lifestyle on Asthma (52) • Dietary reduction of calorie intake on asthma (52) Dietary sodium manipulation (54) • dietary intake of marine n-3 fatty acids by increased fish intake for asthma (30) • **Supplementation** • Dosage and effects of Vitamin C and E (56) • vitamin C for exercise-induced asthma (59)	There is also a need for longer intervention as well as follow-up durations to evaluate the effect of sustained measures to achieve weight loss and to determine if these effects are still significantly present after a considerable period of time (57).
Comparison	• Placebo (59,59) • placebo interventions (such as dummy mattress cvers) (61) • Vitamins C and E versus vitamin C alone, or versus vitamin E alone (56). • Direct head-to-head comparative trials of mono and multifaceted allergen reduction strategies (61)	There is also a need for direct head-to-head comparative trials of mono and multifaceted allergen reduction strategies (61)

	Outcome	• Quality of life (30,52,56–59) • Exacerbation rates (30,56,59) • Adverse effects (56,57,59). • Bronchoconstriction (56,58), • Exercise tolerance (56) • Asthma symptom scores (55) • Impact on work and school (56) • Asthma symptoms/control (30,57) • Use of rescue medication (57), • Hospital utilization or admission (30,57) • Patients' perception of the effect of caffeine (58) • Utilize guidelines for diagnosing asthma for the study outcome (61) adequate measurement and recording of symptoms e.g. lung function,(52,55–57,59) • Standardised rating scales and outcome measures (53)	Future randomised placebo control trials should include the following outcomes robust symptom recording, HRQL , exacerbation rates and adverse effects (56)
	Study design	<u>Design in Primary Study</u> • RCTs (56,57,59,61) • High Quality Trials (56,57,59) • Larger studies or adequately powered studies (30,52–56,59,60) • Direct head-to-head comparative trials of mono and multifaceted allergen reduction strategies (61) • Blinding and allocation concealment (55,57) (55,61), • Economic evaluation/cost effectiveness studies (61)	1.Larger randomised trials are required in further research for selenium treatment for asthma (53)
	Timeframe	• Long term follow up (52) (57) (61) • Changes that persist longer than two weeks (54)	There is also a need for longer intervention as well

			as follow-up durations to evaluate the effect of sustained measures to achieve weight loss and to determine if these effects are still significantly present after a considerable period of time (57)

Table a12: Research Gaps for Cochrane nutrition reviews addressing diabetes

Table a12 shows the detailed summary of the research gaps identified in the "implications for research" section of Cochrane nutrition reviews addressing diabetes. The first column (NCD grouping) is the NCD grouping diabetes being addressed. The second column (Domain) is the EPICOT+ Framework item i.e. population, intervention, comparison, outcome, study design and time frame. The third column is the research recommendation for which future research should address e.g. people with type 2 diabetes. The number in the brackets e.g. (105,106) is the citation of review(s) (found in the References list (Section 7)) which have made that particular future recommendation. The fourth column (Example) is an example of the text from the "implications for research" section from which we identified the research gaps.

NCD Grouping	Domain	Recommendation	Example
Diabetes	Population	• Children (106,108) • Older patients with diabetes (110) • People with type 2 diabetes (102,111) • Patients with both type 1 and type 2 diabetes (97,107,109) • Individuals with "normal" BP (11) • Individuals with early development of DKD (11) (112) • Participants with a higher mean baseline HbA1c greater than 8% (103) (121) (110) • Persons not currently overweight (101) • Genetic subgroups of the population at risk of diabetes (105)	There currently persists a research gap in the literature that investigates the effect of cinnamon in young children (108)
	Intervention	**Foods** • Role and mechanisms of omega-3 PUFA (99) • Other species and parts of sweet potato (111) • Modality of administration of cinnamon (108) , • Different cinnamon extraction and preparation (108)	Future research should explore other species of cinnamon and different parameters of

	• Other species of cinnamon (108) • Whole grain foods (105)	administration, extraction and preparation (108)
	Dietary patterns and advice • Exercise with reduced energy diet (102) • Low-fat/high carbohydrate diet, modified-fat diet, restricted protein diet etc.) (102) • Frequency of dietary advice (102) • Style of dietary advice (addition of behaviour modification or not) (102) • Usual diet (unrestricted protein) versus reduction to say 0.8 g/kg/day (with chicken and fish instead of red meat) versus a vegetarian diet with no restriction in protein versus a vegetarian diet with modest intake (1 g/kg/day) (97) • More modest, sustained salt reduction (11) • Effect of diet plus physical activity (98) • Empact of low glycaemic index diets (106)	
	Nutritional education and counselling programmes • Impact of individual diabetes patient education (103)	
	Supplementation • Dosage of different vitamin B preparations (112)	
	Other • Different treatments for Type 2 diabetes (100) • Novel approaches to prevent or regress retinal lesions (107) • Sustained interventions for weight loss (101) • Additional treatments for glucose control (109) • Explicitly 'prescribe' interventions for trials (110)	

	• Rormulation of intervention active ingredients (behaviour change techniques) (110) • Dose of intervention (frequency and intensity of interactions) (110) • Modality of administration of intervention (mode of delivery - Internet, mobile phone etc) and duration of treatment (110)	
Comparison	• usual diet (unrestricted protein) versus reduction to say 0.8 g/kg/day (with chicken (97) • fish instead of red meat) versus a vegetarian diet with no restriction in protein versus a vegetarian diet with modest intake (1 g/kg/day) (97) • individual diabetes patient education vs group education (103) • vitamin B compared to placebo or losartan (112)	There is a lack of evidence of short-term or long-term benefits of vitamin B compared to placebo or losartan on clinical and biochemical outcomes (112)
Outcome	• mortality (102,104) • quality of life (97,100–102,104,106) • incidence of type 2 diabetes mellitus (104), • adverse events (106) • insulin resistance (104), • glomerular filtration rate (GFR) (97) • cardiovascular risk factors such e.g. lipids (97) • surrogate markers of kidney function (urinary albumin) (11) • emerging cardiovascular risk markers in type 2 diabetes (99) • change (or delay) in onset of anti-diabetic medication (102) • Reliable and validated measures of cognitive function (100) • long-term complications of T2DM (111) (98) • long-term glycaemic control (106) • efficacy and safety profile of vitamin B therapy (112) • depression, weight loss, physical activity and blood lipid profiles (110) • relevant intermediate endpoints for type 2 diabetes (105) • sustained interventions for weight loss and control (101) • measures of the presence and severity of neuropathy (109)	Outcomes should include all of glomerular filtration rate (GFR), quality of life, cost-effectiveness and cardiovascular risk factors such as lipids (97).

Study Design	<u>Design in Primary study</u> • Trials (97–99,103–105,107,108,111,112) • High quality studies (99,103,105,108,111,112) • Larger number or adequately powered studies (99,103,111) • Economic evaluation or cost-effectiveness studies (97,101,108,110) • Observational trials (111) • Evidenced and scientific based interventions following systematic and scientific design (110) • High quality trials with (allocation concealment, minimization of attrition, follow-up of dropouts, comparison of dropouts to completers at baseline, and ITTanalysis (101). <u>Reporting in Primary study</u> • Clarity on reporting of adverse effects (111)	In future, high quality RCTs are needed to establish efficacy and safety profile of vitamin B therapy especially treatment used in addition to the first line treatment (112)
Time Frame	• Long-term studies (76)(99,105)(99,111) (97) (103) (110) • Long-term use dietary advice (102) Outcome measures that capture short- and long-term outcomes (108) • Long-term glycaemic control (106) • Short-term or long-term benefits of vitamin B compared to placebo or losartan (112) • Long-term weight loss interventions (101)	Studies with longer follow-up are needed to determine the long-term impact on health outcomes of these interventions and look for evidence of harm (110)

Table a13: Research Gaps for Cochrane nutrition reviews addressing obesity and overweight

Table a13 shows the detailed summary of the research gaps identified in the "implications for research" section of Cochrane nutrition reviews addressing obesity and overweight. The first column (NCD grouping) is the nutrition-related risk factor obesity and overweight being addressed. The second column (Domain) is the EPICOT+ Framework item i.e. population, intervention, comparison, outcome, study design and time frame. The third column is the research recommendation for which future research should address e.g. children aged 0-3 years. The number in the brackets e.g. (122) is the citation of review(s) (found in the References list (Section 7)) which have made that particular future recommendation. The fourth column (Example) is an example of the text from the "implications for research" section from which we identified the research gaps.

NCD Grouping	Domain	Recommendation	Example
Overweight and Obesity	Population	• Young children aged 0-3 years (37) • Children aged six to 12 years (37) • Adolescents (37) • Obese parents and their children (121) • Children and adolescents with obesity or overweight (117) • Children in preschool years and puberty (117) • Ethnicity, e.g. children from minority ethnic groups (121) • Parents in pediatric obesity intervention studies (121) • Overweight and obese adults (115) (33) • Patients and healthcare professionals (33)	More evidence is needed to determine effective interventions in young children, particularly those aged 0-3 years, and adolescents (37)
	Setting	• Healthcare setting (33) • Low- and middle-income countries (33,37,117,121) • Faith-based settings (37)	We do recommend that further research in the early years and adolescence is conducted,

	• Clinical setting (117)	and that research should include a wider range of community settings (including faith-based settings) 37)
Intervention	**Foods** • Detailed description of Dosage and composition of chitosan (34) and green tea (116) **Nutrition education and counselling programmes** • Educational interventions other than brief face-to-face meetings (33) • Use of e-health systems in weight management, using distal measuring devices (33) • Use of smart phone functions in weight management (113), • Evidence-based (clinical) interventions (33) • Effectiveness of the TTM SOC (115) **Dietary Patterns** • Effects of different diet-only interventions (119) • Effectiveness of physical activity, dietary and other behavioural interventions (117) **Other** • Clear and detailed descriptions of the intervention(s) (115)	Further research is also needed into the effects of different diet-only interventions (119)
Comparison	• New interventions to be compared to 'standard care (33)	Future studies should ensure that innovative interventions are always

		compared to 'standard care' (33)
Outcome	• Adverse effects (113,116,119,121) • Quality of life (34,113,116,120,121) (115), • Morbidity (34,118) • Mortality (34) • BMI (or zBMI) (37) • Obesity-related comorbidities (120) • Risk factors for cardiovascular disease, e.g. high blood pressure, lipid, new diagnoses of type 2 diabetes (33) • Self-esteem (121), • Prevalence of overweight (37) • Mean and standard deviation for outcomes (37) • Effects of CrP in preventing overweight and obesity (118) • Activity behaviour change (120) • Brain-imaging techniques (117) • Clear and detailed descriptions of outcome measures (115) • Standards for measuring and reporting adherence (e.g kilograms lost (114)	Future studies should include outcomes such as health-related quality of life and adverse effects (116)
Study Design	<u>Design of Primary Study</u> • Trials (33,34,115,117,118,121) • Qualitative research (120) • Systematic review of non-randomised controlled trials (115) • Study designs other than randomised controlled trials (120)	Future studies should follow a standard reporting format, such as CONSORT ,to ensure that all details of the study are available for assessment and perform an ITT and per protocol

		• High Quality studies (randomisation, allocation concealment, blinded and intention to treat analysis and power calculations) (33,34,115,121) • Large/adequately powered studies (115,117) • Economic Evaluation/cost effective studies (33,34,37,121) • (33,34,121) • Methods to impute missing outcome data (117) • ITT and per protocol (PP) analysis (116) • Use a protocol when conducting and reporting research (115) <u>Reporting in Primary study</u> • Adopting Consort guidelines (33,116)	(PP) analysis to account for drop-outs after randomisation (116)
	Time frame	• longer-term follow-up studies (37) (117) 129) (126)(115) (114) (113)	We suggest that interventions and strategies to prevent obesity in children should include follow-up over several years (37)

Table a14: Research gaps for Cochrane nutrition reviews addressing healthy diets

Table a14 shows the detailed summary of the research gaps identified in the "implications for research" section of Cochrane nutrition reviews addressing healthy diets. The first column (NCD grouping) is the nutrition-related risk factor being addressed i.e. healthy diets. The second column (Domain) is the EPICOT+ Framework item i.e. population, intervention, comparison, outcome, study design and time frame. The third column is the research recommendation for which future research should address e.g. children aged five years and under. The number in the brackets e.g. (133) is the citation of review(s) (found in the References list (Section 7)) which have made that particular future recommendation. The fourth column (Example) is an example of the text from the "implications for research" section from which we identified the research gaps.

NCD Grouping	Domain	Recommendation	Example
Healthy Diets	Population	• Children aged five years and under (123) • Culturally diverse backgrounds (eg. Indigenous people)	The investigation of the impact of interventions for children from low-income, minority or indigenous communities (including by subgroup analyses) (123)
	Setting	• Heath services and sports clubs (123) • Low-income, minority or indigenous communities (123) • Sports settings (122) • Preschools, play-groups, sports clubs, or co-operatives, (123)	Future interventions should include interventions implemented across a broader range of settings including heath

			services and sports clubs (123)
	Intervention	• Different electronic modalities such as the web or mobile phones (123) • Behavioural interventions delivered by health professionals, telephone- or computer-based programmes (123) • Interventions delivered through preschools, play-groups, sports clubs, or co-operatives (123) • Clear definition and description of intervention (124) • Interventions with sound theoretical base which is explicitly reported in the publication (122) • Interventions that are based on logic models of change, appropriate theoretical frameworks and evidence (123)	Further studies are now essential to refine methods for providing dietary advice and improve diet adherence in the context of chronic diseases(124).
	Comparison	• intervention group vs control/usual care group (124) • adequate control group consisting of a matched sporting organization (122)	Further research with a comparison between an intervention group and a control/usual care group both providing the same dietary advice to capture the effect of the intervention only, without confounding factors is required (124)
	Outcome	• adverse effects (e.g. increased family grocery costs, adverse effects on parent self-esteem or sense of competence) (123) • Psychosocial, environmental determinants and biological factors affecting food intake (124)	Future trials should incoperate investigation of potential adverse effects of interventions (e.g.

		• perspectives from health professionals and clients about the interventions enhancing adherence (124) • standardized and validated self-report tools and robust objective measures (e.g. biomarkers) to assess adherence to dietary advice (124) • Development of policies, implementation of policies and changes in individual behaviour relating to the particular policy (122) • Use of tools validated to measure outcomes (such as sun protection habits, alcohol use, smoking status, frequency of healthy eating, etc) (122) • Behavior change (122)	increased family grocery costs, or adverse effects on parent self esteem or sense of competence) as a routine part of intervention trials (123)
	Study Design	<u>Design of Primary study</u> • High quality trials (123,124) • Economic evaluation/cost effective studies (123) • Factorial design studies (for policy interventions) (122) • Repeated measurements before and after design (122) • Further studies designed to minimise bias (124) • Cluster design with adequate sample size per cluster (122)	Future trials should include examination of the cost-effectiveness of interventions found to be effective (123).
	Time frame	• Interventions with extended periods of follow-up (123) (124)	Further studies with a long-term duration of more than 12 months, and a follow-up evaluation are needed (124).

PART B: **Appendices**

Addendum

Instruction to Authors for the BMC Medical Research Methodology Journal

Preparing main manuscript text

- Use double line spacing
- Include line and page numbering
- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF
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Preparing the manuscript

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The title page should:

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  - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
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Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field

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The methods section should include:

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- the characteristics of participants or description of materials
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- the type of statistical analysis used, including a power calculation if appropriate

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This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

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Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

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Acknowledgements

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Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

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Research Project Protocol

Stellenbosch University

Faculty of Medicine and Health Sciences

Division of Community Health

MSc Clinical Epidemiology Research Project Proposal

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Title: Identifying Gaps in Primary Nutrition Research from Cochrane Nutrition Reviews using the EPICOT+ Framework

30 September 2016

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Table of Contents

1. Background

Non-communicable diseases: burden and risk factors

Non-communicable Diseases (NCDs) are medical conditions or diseases that are non-infectious and not transmissible between people (1). NCDs are commonly categorised into the following groupings: cardiovascular diseases, cancer (all types), chronic respiratory diseases (e.g. asthma, bronchitis), diabetes (type 1 and 2), renal disease, endocrine disease, neurological disorders, haematological disorders (e.g. sickle cell anaemia), gastroenterological disease (e.g. peptic ulcers), hepatic disease (e.g. liver cirrhosis), musculoskeletal disorders, skin diseases, oral diseases, genetic disorders, mental disorders, optometry disorders and deafness (2). The four major groups that contribute to 86% of deaths from NCDs are cardiovascular diseases, cancer, respiratory disease and diabetes (1). In 2012, NCDs accounted for 38 million deaths globally and three quarters of these deaths occurred in low- and middle-income countries (LMICs) (1). It is reported that the prevalence of NCDs is on the rise, especially in LMICs, and the World Health Organisation (WHO) predicts that by the year 2020, 300 million people will be living with NCDs globally (8,197). The WHO recommends that governments and stakeholders adopt effective interventions to halt this global rise in NCDs (2).

Risk factors associated with NCDs largely stem from unhealthy lifestyles and exposure to adverse physical and social environments. Modifiable risk factors include unhealthy diets, direct and passive smoking, other uses of tobacco, physical inactivity, excessive use of alcohol and psychological stress (4–7). Poor nutrition during pregnancy and childhood also predisposes individuals to develop NCDs later in adulthood (8). Knowledge of the modifiable risk factors contributing to NCDs presents an opportunity to find effective interventions to reduce the incidence of NCDs (4). A vast body of observational and experimental evidence has shown that people with healthier diets have a lower risk of developing NCDs. A meta-analysis of nine cohort studies (n=91,379 men and n=129,701 women) reported that the risk of developing coronary heart disease decreased by 4% [RR (95%CI): 0.96 (0.93–0.99), P<0.0027] for each additional portion per day of fruit and vegetable intake and

decreased by 7% [RR (95%CI): 0.93 (0.89–0.96), P<0.0001] for fruit intake (5). Vegetable intake also reduced the risk of mortality [RR (95%CI): 0.74 (0.75–0.84), P<0.0001] and fatal and nonfatal myocardial infarctions [RR (95%CI): 0.95(0.92–0.99),P<0.0058] (5). Another systematic review of randomised control trials found that reducing the consumption of dietary saturated fat reduced the risk of cardiovascular events by 17% [RR (95%CI) 0.83 (0.72 to 0.96)] in individuals regardless of whether they had a previous cardiovascular event or not (10). The evidence from these and other studies demonstrates the potential for lifestyle interventions, including those addressing dietary risks, to prevent NCDs.

In light of the above evidence and the need to adopt interventions that are effective in halting the rise in NCDs globally, and especially in LMICs, the WHO proposed a Global Action Plan for the prevention and control of NCDs (2). This action plan highlights the need to use strategies based on the latest scientific evidence and/or best practice, cost-effectiveness, affordability and public health principles, while ensuring that recommendations are culturally acceptable (2).

Systematic reviews as sources of evidence and to identify research gaps

The best available evidence is commonly considered to be from rigorously conducted and reported systematic reviews. Cochrane systematic reviews are regarded as high quality sources of synthesised scientific evidence, as they follow robust and standardised methodology (15). Cochrane systematic reviews attempt to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question (198). Studies that fit the inclusion criteria undergo an assessment of methodological quality to evaluate the extent to which bias was avoided. The characteristics and findings of the included studies are then synthesized, presented and reported with consideration of the methodological quality of included studies. Some systematic reviews include a meta-analysis; a process that uses statistical methods to combine the results of independent studies to provide more precise estimates of the effects of an intervention than those

derived from the individual studies (198). Meta-analyses also facilitate investigations of the consistency of evidence across studies and exploring differences between studies (198). Cochrane nutrition reviews may thus serve as a source of high quality evidence to identify strategies that will help to prevent and control NCDs globally.

In Cochrane reviews authors are required to include sections about the implications for practice and research in light of the evidence that has been synthesised in the review; information that is used increasingly often by people making decisions about future research (198). The "implications for research" section should include information about the need for further research, as well as the desirable nature of this research (199). Even though the extent to which this section is completed in Cochrane reviews is variable, most reviews identify residual uncertainty and are a rich source of suggestions for further research (17). Analysing the content of the "implications for research" section of Cochrane reviews can help inform primary research gaps in this area, as well as identify interventions for which the evidence is conclusive and thus do not require further research (18). The problem, however, is the variability in formulating and reporting research recommendations by different systematic review authors (19).

The EPICOT+ framework was developed to provide a means of standardised reporting of recommendations under the "implications for research" section of reviews (20). According to the EPICOT+ framework, research recommendations should be made in consideration of the current state of evidence (E) found by a thorough up to date literature search, the number of systematic reviews and primary studies being analysed and the total number of the participants from the reviews. Other factors to consider when making recommendations include the population (P) being studied (type of participants, their age, race, gender, comorbidities and specific inclusion criteria), the intervention (I) being tested (type, dose, frequency, duration), the comparison (C) (placebo, other drugs or no intervention, duration), the outcome of interest (O) and the time stamp (T) (i.e. the date at which the recommendations are made). The "+" refers to the study design and the

burden of the disease of interest, which are additional elements to be considered and stated clearly when formulating recommendations. Apart from allowing for the formulation of recommendations in a standardised manner, using the EPICOT+ framework ensures that recommendations are specific and explicit and thus more useful (20).

Internal Validity and reporting conflicts of interest in Cochrane Reviews

For valid interpretation and application of systematic review findings, high methodological quality is a prerequisite. A Measurement Tool to Assess Systematic Reviews (AMSTAR) has been developed to assess the methodological quality of systematic reviews (200). The AMSTAR tool has been tested and shown to have good agreement, reliability, construct validity and feasibility compared to other tools that assess methodological quality, such as the Overview of Quality Assessment Questionnaire (OQAQ) and the Sacks' instrument (201). The AMSTAR tool aims to ensure that bias was avoided during the conduct of systematic reviews, through evaluating the methodology reported against 11 distinct criteria (200). For each criterion on the checklist, a “Yes” is regarded as adequate, except for item 4 where the adequate answer is “No”. A score of one is assigned for each adequate response and the scores are added up to give a total that ranges from zero to a maximum of eleven. The quality of reviews is then graded according to their total score: low quality (0-4), moderate quality (5-8) and high quality (9-11) (202).

According to the AMSTAR tool checklist, item 11 requires that conflicts of interest (COI) and sources of support be clearly acknowledged in both the systematic review and the primary studies included in the reviews (201). Conflict of interest is defined as a set of conditions in which professional judgment concerning a primary interest (such as a patient’s welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain) (19). Most systematic review

authors report their COI and sources of funding for the review, however, a recent analysis found that only 21/296 (7%) reviewers reported the COI or funding sources of the primary studies included in their reviews (26). This has important implications since the outcome of the study and interpretation of study findings may be influenced by the source of funding and author-sponsor financial ties (22). A cross-sectional study explored the relationship between financial sponsorship and study conclusions on the benefits of milk, soft drinks and juice from interventional studies, observational studies, and scientific reviews (27). None of the interventional studies that received industry funding reported unfavourable conclusions whilst 37% of the studies that did not receive industrial funding reported unfavourable conclusions about milk, soft drinks and juice consumption. Another study showed that studies reporting a favourable outcome were 7.61 times more likely to have received industry funding compared to the studies reporting an unfavourable outcome (21). A study of published systematic reviews assessing the effect of sugar-sweetened beverages (SSB) consumption and weight gain or obesity found that reviews which reported COI were five times more likely to present a conclusion of no positive association between SSB consumption and weight gain than reviews which did not report COI [RR (95%CI): 5.0 (1.3–19.3)] (29). These studies provide evidence that financial ties between study authors and funders may influence how authors interpret study findings. This highlights the need for review and primary study authors to declare COI and study sponsor information and affiliation when reporting studies.

With the rise in NCDs globally, there is a need to identify research gaps in the primary evidence base on nutrition interventions that may be useful to control the NCD burden. Cochrane nutrition reviews on NCDs provide the best scientific evidence to inform further research; however, there is a need to explore how review authors report recommendations and identify areas that need improvement to achieve standardised and more useful reporting of recommendations. In this study, we aim to analyse the “implications for research” section of Cochrane nutrition reviews to identify gaps in primary evidence, to explore the reporting of COI, and to explore the association between financial COI and the findings of study in the primary studies included in these reviews. The aims of this

project are in line with the key objectives of the recently established Cochrane Nutrition field in South Africa. These objectives include examining the use of nutrition systematic reviews to inform the research agenda for new primary studies and systematic reviews, increasing the impact of Cochrane nutrition reviews across all stakeholders and enhancing the methodology of Cochrane nutrition reviews.

2. Objectives

1. To describe the reporting of the "implications for research" section of Cochrane nutrition reviews addressing NCDs according to the EPICOT+ framework

2. To summarize current gaps in primary research based on the "implications for research" section of Cochrane nutrition reviews addressing NCDs

3. To assess the reporting of COI and financial sponsors in included English primary studies of a random sample of Cochrane nutrition reviews addressing NCDs

4. To explore the influence of author-sponsor financial ties and funding source on study outcomes and interpretation of the study outcomes in included English primary studies of a random sample of Cochrane nutrition reviews addressing NCDs

For this project, we will only include reviews addressing the four major groups of NCDs, namely cardiovascular diseases, cancer, respiratory disease and diabetes and their nutrition-related risk factors (e.g. obesity).

3. Methods

3.1 Study Design

This will be a cross-sectional descriptive study analysing the implications for research section of Cochrane nutrition reviews addressing the four major groups of NCDs to identify knowledge gaps in the evidence base, and to assess the reporting of COI and funding sources in primary studies included in a sample of these reviews will be assessed.

3.2 Data Source

The source of systematic reviews for this study is a database of Cochrane nutrition reviews. This database was compiled for a previous project, in which all active records in the Cochrane Database of Systematic Reviews (n=8484) up to 31 July 2015 were screened to identify all nutrition reviews using a pre-specified definition. Nutrition reviews were defined as those that investigate the effectiveness of interventions of:

(1) Diets and dietary patterns; foods; formulated, fortified or enriched foods or nutritional products and nutrients and bioactive non-nutrients naturally in foods delivered orally, enterally or parenterally;

(2) Nutrition education, promotion, counselling and programmes; coordination of care or delivery of foods or nutrients;

(3) Any policies, programmes or systems that influence outcomes clearly distinguishable as nutrition-related (nutrition-sensitive).

Screening of reviews using the above definition yielded a total of 470 eligible completed reviews. The methodological quality of all identified reviews has already been assessed using AMSTAR (200).

3.3 Data collection and analysis

3.3.1 Selection of Reviews

Two researchers will independently screen the Cochrane nutrition reviews database (n=470) described above (section 3.2) by title, abstract and full-text to identify all eligible reviews. A review will be considered eligible if it addresses any of the four major groups of NCDs, i.e cardiovascular diseases, cancer, respiratory disease and diabetes or their nutrition-related risk factors (e.g. obesity). Any disagreement on inclusion or exclusion of reviews will be resolved by discussion with a third researcher. Reviews that do not fit the inclusion criteria will be excluded from the study.

3.3.2 Selection of primary studies included in Cochrane nutrition reviews focussing on NCDs

From the eligible Cochrane nutrition reviews selected in section 3.3.1, we will draw a random sample of reviews using an online random sequence generator www.random.org/sequences. The primary studies included in this sample will be accessed for the analysis on the reporting of COI and financial sponsors and on the association between study outcomes and author conclusions. For each review included in the random sample, we will extract the references of the included primary studies from the reference list of the reviews. We will search for the full-texts of these primary studies using the citation, the PubMed ID or the DOI, and download them. In instances where there is more than one reference for the same study in a review, the most recent reference of that study will be selected. Owing to limited resources, only articles published in English will be included in this analysis.

3.3.3 Data Collection

A pair of researchers will independently extract data from the included reviews using a standardized data extraction form (Addendum 1). This form will be piloted on 10 included reviews to evaluate its usability, completeness, and to identify any technical problems, and it will be adjusted accordingly.

Any discrepancies will be resolved by consensus and discussion with a third author if needed. The sections below outline the information that will be extracted from included reviews.

Describing the reporting of the "implications for research" section of Cochrane nutrition reviews according to the EPICOT+ framework

To inform the content analysis of the "implications for research" section we will extract the following EPICOT+ items for all reviews included in this study, as defined in section 3.3.1: participants, intervention, comparison, outcomes, time frame of the study and study design. If an EPICOT+ element is explicitly stated and explained in the recommendations, we will record a "Yes" and if the element is not stated in the implications for research section, we will record a "No" in Table 1 of the data extraction form (Addendum 1).

Identifying current gaps in primary evidence based on the "implications for research" section of Cochrane nutrition reviews

We will record a summary of a recommendation for each EPICOT+ element stated in the in the "implications for research section". The summary of the recommendations for each EPICOT+ element represent the research gaps in the primary evidence base for the particular NCD being addressed in that review.

Reporting of conflicts of interest and funding sources and exploring the influence of author-sponsor financial ties and funding source on study outcomes and interpretation of the study outcomes in included English primary studies of a random sample of Cochrane nutrition reviews on NCDs

We will extract the following information from the full-texts of English primary studies included in the random sample of the reviews: title of study, NCD addressed, NCD group addressed, study design (randomised control trial, experimental non-randomized trials, observational studies). We will also categorise the studies according to whether COI was reported or not, type of funding sources (industry, non-industry, or both), funding source not disclosed or not reported, study not funded, author-sponsor financial ties disclosed, study findings and author conclusions (favourable to sponsor or unfavourable to sponsor).

We will extract the online declaration of interest if it is stated that interests have been declared online. Author-financial ties will be defined as authors who are current/former industry consultants, current/former industry board members, current/former industry employees, receiving royalties, authors receiving travel reimbursement, have other relationships with industry, authors who hold patents (planned, pending, or issued) or authors who provide expert testimony. Information on author-sponsor financial ties will be extracted from statements in acknowledgements, potential conflict of interest statements and/or footnotes. Funding sources for the reviews will be extracted from the sources of support declaration or acknowledgments, and will be classified as industry, non-industry (for example, public granting agency, private not-for-profit granting agency), combined (industry and non-industry), funding not reported, review not funded, review funding information not disclosed. A favourable outcome is where the study favoured the experimental item (intervention) over the existing standard of care, or otherwise arrived at a positive conclusion regarding the item being evaluated in favour of the sponsor. An unfavourable outcome is where the study favoured the existing standard of care or comparator item over the experimental item being evaluated and the conclusion supports the comparator over the intervention or when the item being studied has no superiority over the existing standard or comparator and is not in favour with the sponsor.

3.4 Data Analysis

Data will be analysed using STATA. We will use descriptive statistics and data will be presented as counts and percentages and visually as graphs and tables.

Characteristics of included reviews and primary studies

We will report the screening and selection of Cochrane nutrition reviews and included primary studies in form of a flow chart. The AMSTAR ratings will be tested for normality using Kolmogorov-Smirnov test and if the data is normally distributed we will report the ratings as means and standard deviation, if the data is not normally distributed, we will report the median and inter-quartile ranges. We will report the online date and time stamped random sequence which will be used to select the random sample of reviews for the COI analysis. We will report study title, the counts and proportions of selected reviews according to NCD group (cardiovascular diseases, cancer, respiratory disease and diabetes). We will report the following characteristics in table form for primary studies included in the random sample of Cochrane nutrition reviews: Study title, population, NCD being addressed, NCD grouping (cardiovascular diseases, cancer, respiratory disease and diabetes), participants, intervention, comparison and outcome.

Reporting of the "implications for research" according to EPICOT+ Framework

We will report the number of reviews making recommendations according to the EPICOT+ framework elements: population, intervention, comparison, outcome and time frame of study overall and for each NCD being addressed. The data will be presented as counts and percentages in the form of bar graphs. For example, the total number of reviews that made recommendations considering the population will be expressed as a percentage of the total number of reviews

included in the study. This will be done for each element of the EPICOT+ framework. We will also report the number of reviews that reported all the EPICOT+ framework elements as a percentage of the total number of reviews included in this study. We will give a description of which EPICOT+ framework elements are better or less well reported in the NCD reviews.

Summarising research gaps in primary evidence base

Firstly we will report the research gaps extracted from the implications for research section for each specific NCD and risk factors that fall within the 4 major groups (cardiovascular diseases, cancer, respiratory disease and diabetes), from the summaries of recommendations for each EPICOT+ element reported in the review section. We will highlight the participants, intervention, outcome, specific study design and length of time which further primary research should focus on. Secondly, we will report the "implications for research" data for each NCD according to the following categories: no more studies required, more studies required overall, more studies required with better quality, more studies required in different settings, more studies required in different populations, more studies with different interventions, more studies with different outcomes, more studies with longer follow up and further evidence unlikely to come from studies. We will give the counts and percentages of each category of "implications for research" according to the NCD being addressed. These data will be present in form of a graph and table.

Influence of funding source and author financial affiliation on study outcomes in English included primary studies of the random sample of Cochrane nutrition reviews

The data on the following characteristics of included primary studies will be presented as counts and percentages of the total number of included primary studies: reporting of conflict of interest (e.g. number of studies that reported COI / total number of English included primary studies) , disclosure

of author-financial sponsor ties, number of authors with author-sponsor financial ties, type of study sponsor (industrial, non-industrial, both industrial and non –industrial), study sponsor not reported, study outcome and conclusion by authors (Favourable to sponsor and Unfavourable to sponsor). We will group the included primary studies according to the study outcome (Favourable outcome sponsor and unfavourable outcome to sponsor) and report the frequency of included primary studies that reported or did not report COI, disclosed author-sponsor affiliation ties and the frequency of each type of study sponsor (industrial, non-industrial, both industrial and non – industrial) in form of a bar graph. To measure the association between the type of study sponsor and study outcome and author conclusions and the association between author-sponsor financial ties and study outcome and author conclusions, we will do multiple logistic regression analysis that will include potential predictors to estimate adjusted odds ratios. The model will include the following variables: conflict of interest, author-sponsor financial ties, type of study sponsor and study design.

3.5 Ethical Considerations

Since there will be no direct involvement of human or animal participants, there is no need to seek ethical approval for this study.

3.6 Limitations

The reviews considered in this study are from one source (Cochrane nutrition reviews) hence there might be a limited scope for nutrition and NCD topics covered. We only focussed on included studies that have been published in English only which poses a selection bias.

4. References

1. WHO | Global Action Plan for the Prevention and Control of NCDs 2013-2020 [Internet]. WHO. [cited 2016 Jul 14]. Available from: http://www.who.int/nmh/events/ncd_action_plan/en/

2. Terzic A, Waldman S. Chronic Diseases: The Emerging Pandemic. Clin Transl Sci. 2011 Jun 1;4(3):225–6.

3. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJL, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet Lond Engl. 2002 Nov 2;360(9343):1347–60.

4. Wang S, Marquez P, Langenbrunner J. Toward a healthy and harmonious life in China : stemming the rising tide of non-communicable diseases [Internet]. The World Bank; 2011 Jul [cited 2016 Jul 21] p. 1–48. Report No.: 63426. Available from: http://documents.worldbank.org/curated/en/2011/07/14639951/toward-healthy-harmonious-life-china-stemming-rising-tide-non-communicable-diseases

5. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and Vegetable Consumption and Risk of Coronary Heart Disease: A Meta-Analysis of Cohort Studies. J Nutr. 2006 Jan 10;136(10):2588–93.

6. Hardy ML, Duvall K. Multivitamin/multimineral supplements for cancer prevention: implications for primary care practice. Postgrad Med. 2015 Jan 2;127(1):107–16.

7. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes, Cardiovascular Disease, and Weight Gain. J Nutr. 2012 Jan 7;142(7):1304–13.

8. Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. In: Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 2015 [cited 2016 Sep 26]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011737/abstract

9. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996 Jan 13;312(7023):71–2.

10. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2016 Aug 14]. Available from: http://handbook.cochrane.org/

11. 12 Interpreting results and drawing conclusions [Internet]. [cited 2016 Jul 22]. Available from: http://handbook.cochrane.org/chapter_12/12_interpreting_results_and_drawing_conclusions.htm

12. Clarke L, Clarke M, Clarke T. How useful are Cochrane reviews in identifying research needs? J Health Serv Res Policy. 2007 Apr;12(2):101–3.

13. Lavis JN, Posada FB, Haines A, Osei E. Use of research to inform public policymaking. Lancet Lond Engl. 2004 Nov 30;364(9445):1615–21.

14. Mbuagbaw L, Kredo T, Welch V, Mursleen S, Ross S, Zani B, et al. Critical EPICOT items were absent in Cochrane human immunodeficiency virus systematic reviews: a bibliometric analysis. J Clin Epidemiol. 2016 Jun;74:66–72.

15. Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. BMJ. 2006 Oct 14;333(7572):804–6.

16. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15;7:10.

17. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013–20.

18. Seo H-J, Kim KU. Quality assessment of systematic reviews or meta-analyses of nursing interventions conducted by Korean reviewers. BMC Med Res Methodol. 2012 Aug 28;12:129.

19. Petryna A. Ethical variability: Drug development and globalizing clinical trials. Am Ethnol. 2005 May 1;32(2):183–97.

20. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. PLOS Med. 2016 May 24;13(5):e1002028.

21. Schott G, Pachl H, Limbach U, Gundert-Remy U, Ludwig W-D, Lieb K. The financing of drug trials by pharmaceutical companies and its consequences. Part 1: a qualitative, systematic review of the literature on possible influences on the findings, protocols, and quality of drug trials. Dtsch Ärztebl Int. 2010 Apr;107(16):279–85.

22. Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between Funding Source and Conclusion among Nutrition-Related Scientific Articles. PLOS Med. 2007 Jan 9;4(1):e5.

23. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA. Financial Conflicts of Interest and Reporting Bias Regarding the Association between Sugar-Sweetened Beverages and Weight Gain: A Systematic Review of Systematic Reviews. PLOS Med. 2013 Dec 31;10(12):e1001578.

6. Addendum

1: Data Extraction form

1.1 General information

Title of Systematic Review

Non communicable disease group

Non Communicable Diseases

Table 1: Describing the reporting of "implication of research" according to the EPICOT+ framework.

EPICOT Element			Summary of implications for research recommended
Participants	Yes	No	
Intervention	Yes	No	
Comparison	Yes	No	
Outcomes	Yes	No	
Time stamp	Yes	No	
Study Design	Yes	No	

Table 2: Characteristics of English included primary studies of the randomly selected sample of Cochrane nutrition reviews on NCDs.

Data domain	Variables	

Study designs	• **Randomised controlled trials**
	  • parallel
	  • cross-over design;	

	• **Experimental non-randomised studies**
	  • non-randomised controlled trials,
	  • controlled before-after studies,
	  • interrupted time series
	  • repeated measures studies	

	• **Observational studies**
	  • cohort,
	  • case-control,
	  • cross-sectional)	

Primary Study title		
NCD being addressed		
NCD group		
Number of authors		
Reporting of conflict of interest	• Reported	
	• Not reported	
Disclosure of author- sponsor financial ties	• Disclosed	
	• Not Disclosed	
Number of authors with author-sponsor ties		
Type of sponsor	• industrial,	
	• non-industrial,	
	• both industrial and non – industrial,	
	• not reported	
Study outcome and conclusion by authors	• Favourable to sponsor	
	• Unfavourable to sponsor	

Table of Data Extraction Domains

Selection of Cochrane Nutrition Reviews
Cochrane Review Accession Number
Title of Cochrane Review
Withdrawn Cochrane Review
Complete Cochrane review
Selection of Nutrition Reviews by SR
Independent and duplicate selection of Nutrition reviews by CN and SD
Cochrane Reviews addressing alternative nutrition supplements
Cochrane Reviews addressing alternative nutrition supplements with included primary studies
Number of included Primary Studies in Cochrane Reviews addressing alternative nutrition supplements
EPICOT+ Framework analysis for Cochrane Reviews and Research Gaps analysis
Cochrane Review Accession Number
Title of Cochrane Nutrition Review
Non-communicable diseases
Non-communicable diseases grouping
Risk Factor
Brief description of Participants, interventions, comparison and outcomes being addressed in the review
Evidence
Description of Evidence (Implications for research section text)
Population
Description of Population (Implications for research section text)
Intervention
Description of Intervention (Implications for research section text)
Comparison
Description of Comparison (Implications for research section text)
Outcome
Description of Outcome (Implications for research section text)
Last date of literature search
Study Design
Description of Study Design (Implications for research section text)
Burden of disease
Description of burden of disease (Implications for research section text)
Timeliness (Length of study follow up or duration of study)
Description of Timeliness (Implications for research section text)
Implications for Research analysis for Cochrane Reviews
No more trials required
More Cohort studies required
More Qualitative Studies required

Further evidence most likely not to come from trials
More Systematic Reviews required
More Cost effective and Economic Evaluation studies required
More trials with different comparison required
More long term trials required
More trials with longer duration of follow up required
More trials with larger sample size required
More trials with better quality required
More trials in a different population required
More trials with different interventions required
More trials with different outcomes required
More RCTs required overall
Reporting of Conflict of interest, study financial sponsors and author financial ties and the influence of funding source on study outcome and authors conclusions in included primary studies
Primary study title
Primary study Journal published
Cochrane Review Accession Number (parent Cochrane nutrition review)
Cochrane review title
Non-communicable disease being addressed
Nutrition-related risk factors
Study Site
Population
Intervention
Comparison
Outcome
Study Design of primary study
Country where primary study was conducted
Disclosure of financial sponsor
Role of Financial sponsor mentioned
Name of financial sponsor
Food Industry sponsor
Governmental sponsor
Non Profit sponsor
Big Pharma (Pharmaceutical industry) sponsor
Other for profit entities sponsor
Mixedfundingsources1(with Food Industry)
Mixed funding sources 2 (with Big Pharma)
Mixed funding sources3 (with food industry and Big Pharma)
Mixed funding sources 4 (without industry)
Outcome favourable to Sponsor
Outcome favourable to sponsor justification
Conflict of interest disclosure

Expert testimony
Current or former industry employee
Current or former industry consultant
Industry grants
Non Industry grants
Payment for lectures
Payment for manuscript preparation
Patents (received or yet to be received)
Royalties
Payment for Education courses or degrees
Stock
Travel
Other
Author-financial sponsor ties disclosed
Name of Author –financial sponsor ties
Outcome favourable to author-financial sponsor ties
Outcome favourable to author-financial sponsor ties justification

Acknowledgements

We would like to thank Michael McCaul from the Centre of Evidence base Health Care and Biostatistics and Epidemiology unit Stellenbosch University for his assistance with data analysis

Sources of Support:

Sheena Ruzive acknowledges financial assistance from Prof Lisa Bero, recipient of the 2015 Cochrane Anne Anderson Award, whereby a cash sum was designated by the recipient to assist a woman from a low-resource setting with Cochrane activities.

Sheena Ruzive received a bursary from Novartis SA (Pty) Ltd in 2015 which was used to cover the cost of her Master of Science (Clinical Epidemiology) tuition fees.

Anti-plagiarism software report (Turnitin)